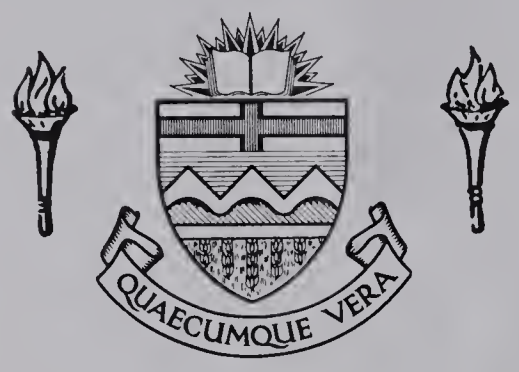
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A TOTAL SYNTHESIS OF 2-O-ACETYL-β-NOVIOSE

BY

© MITREE M. PONPIPOM

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

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submitted by Mitree M. Ponpipom, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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ABSTRACT

Crystalline 2-O-acetyl-β-noviose (XXV) was synthesized by a new method in seven stages in 35% overall yield from the readily available 1,6-anhydro-3,4-O-isopropylidene-β-D-galactose (XI).

β-Noviose 1,2-(methyl orthoacetate) (XXIX) was prepared to study its usefulness as an intermediate for the syntheses of aryl 3-O-acyl-α-noviosides with structures related to the antibiotics novobiocin (I) and coumermycin A_1 (II).

Condensations of 3-O-acetyl-β-noviose 1,2-(methyl orthoacetate) (XXVIII) with two equivalents of a phenol using either antimony pentachloride or mercuric bromide as the catalyst, and phenol and β-naphthol as examples, gave aryl 2,3-di-O-acetyl-α-noviosides in 15-18% yield. When 20 equivalents of phenols were used, the yield of the α-noviosides was about 36%.

Condensations of 3,4,6-tri-O-acetyl-β-D-mannopyranose 1,2-(methyl orthoacetate) (XXX) with two equivalents of phenol using antimony pentachloride or mercuric bromide as the catalyst gave phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI), after acetylation, in 55% and 15% yields, respectively. When 20 equivalents of phenol was

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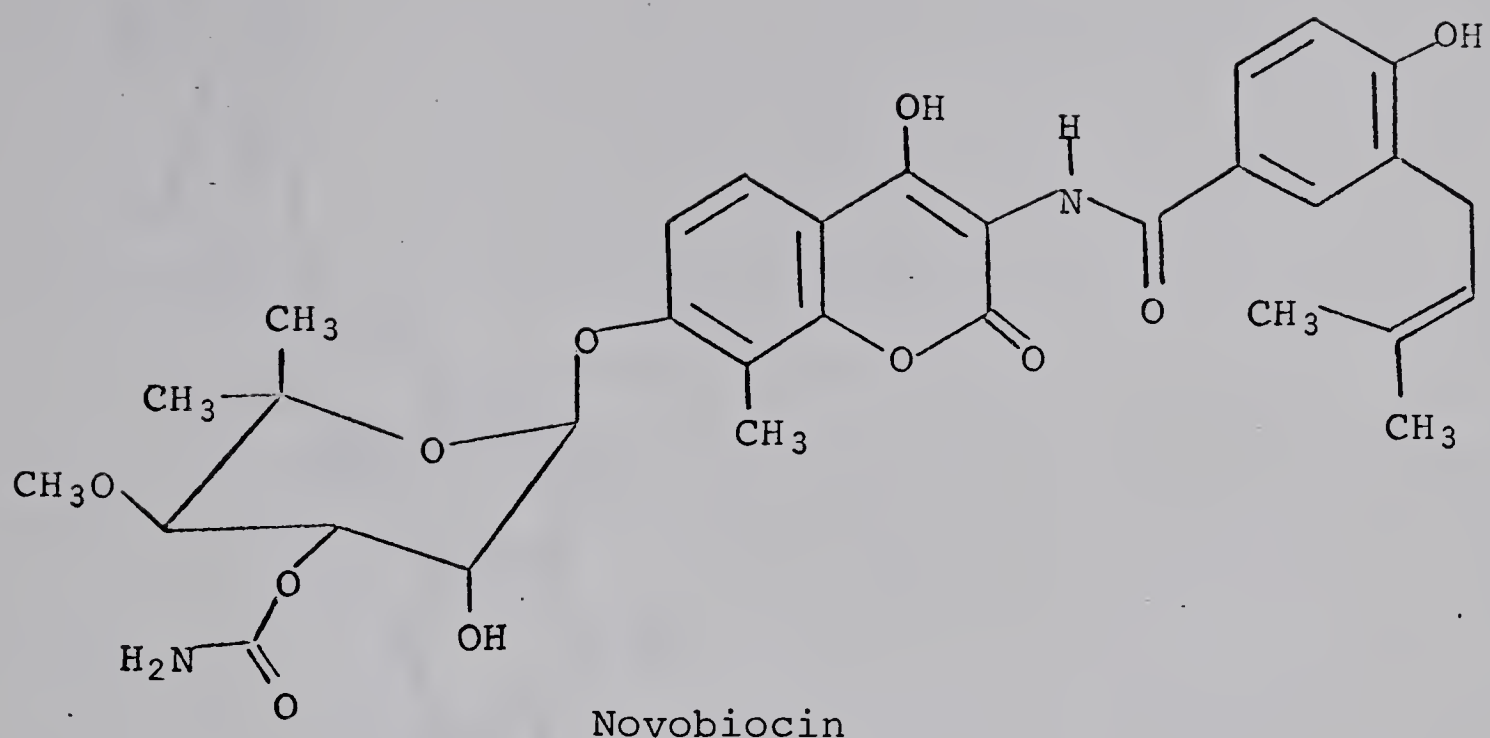
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INTRODUCTION

In 1955, the antibiotic novobiocin (I) was discovered independently in two different laboratories. The Merck group (1) first isolated a compound named cathomycin from Streptomyces spheroides in crystalline form. Their trade name for cathomycin is Cathocin. The Upjohn group (2) discovered streptonivicin from Streptomyces niveus which was isolated originally from a sample of soil collected in Queens Village, New York. Their trade name for Streptonivicin is Albamycin. Cathomycin and Streptonivicin were later shown to be identical (3), and therefore the antibiotic was renamed novobiocin (4). The Pfizer group also isolated the same antibiotic (3) which they called cardelmycin or antibiotic PA-93 from Streptomyces griseus. Novobiocin has since been isolated from a variety of Streptomycete species in many laboratories, and the following names (5) were also used: crystallinic acid, spheromycin and vulcamycin. Novobiocin has found many important therapeutical applications (6). It inhibits the growth of Gram-positive, Gram-negative and acid-fast bacteria.

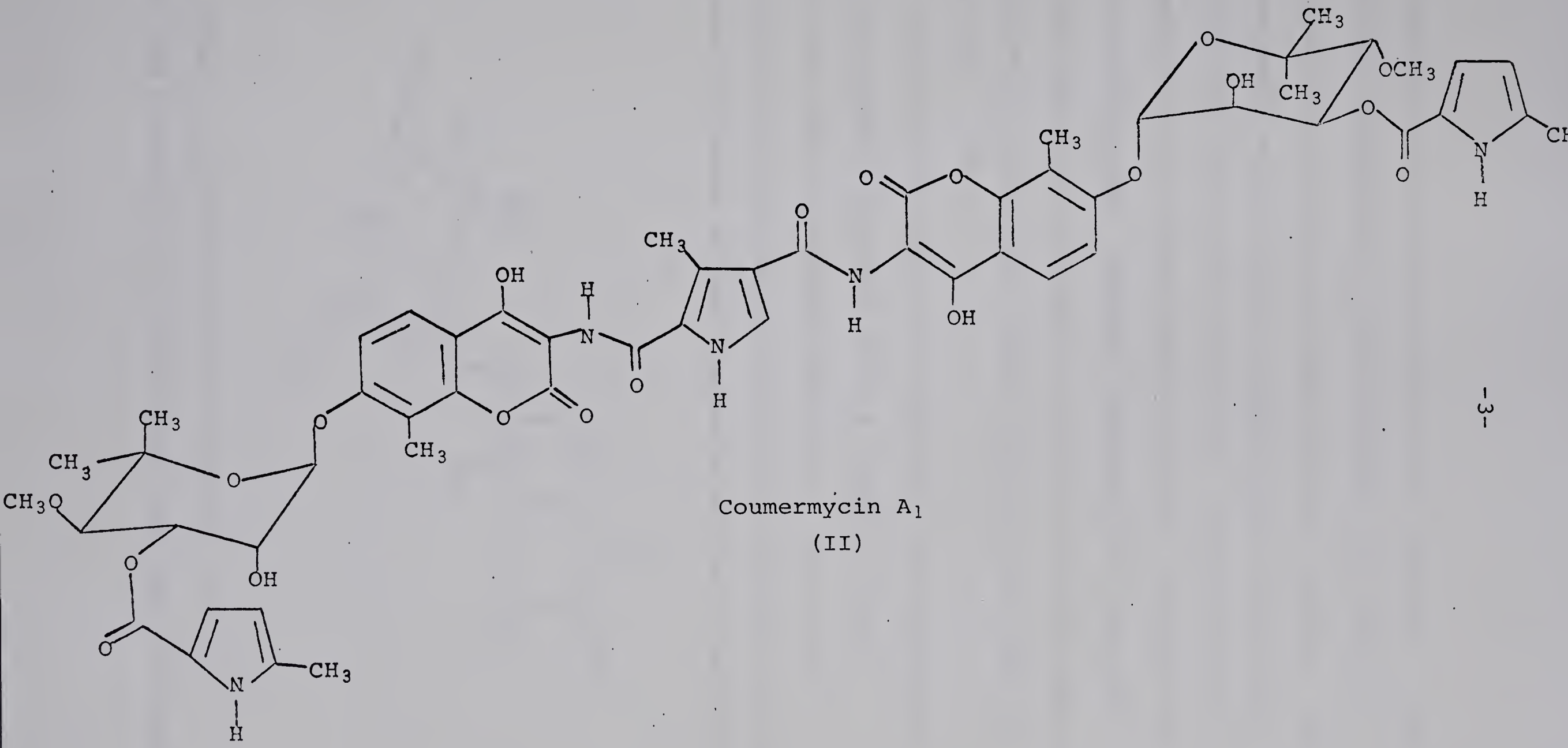


Novobiocin

(I)

The structure of the antibiotic was examined in two laboratories and completed in all details in 1956 (7,8). It appears to be the first recorded example of the natural occurrence of a carbamate ester of a sugar derivative. A number of reviews have appeared (9, 10).

The antibiotic coumermycin A_1 (II) was discovered in 1965 (11) in cultures of Streptomyces rishiriensis which also produced several other antibiotic factors designated as coumermycin A_2, B, C and D. Coumermycin A_1 was found to have a number of structural features in common with novobiocin. As is seen from their structures, the two compounds both have a branched-chain sugar as a building unit and, also, the coumarin portion of their aglycons are identical. The structure of coumermycin A_1 was elucidated

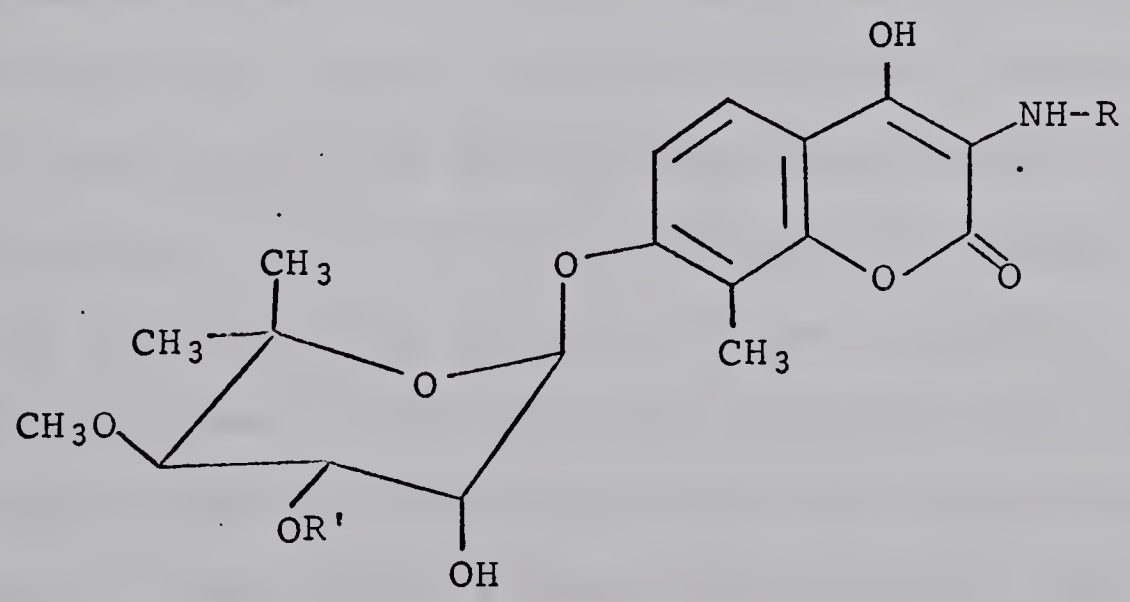


Coumermycin A_1

(II)

by Kawaguchi and co-workers (12) in the same year. Like novobiocin, coumermycin A_1 also inhibits the growth of Gram-positive, Gram-negative and acid-fast bacteria. It is remarkably active against staphylococci, being about 30 times more potent than novobiocin. Like novobiocin, coumermycin A_1 also shows greater activity in acidic pH than in alkaline pH. However, coumermycin A_1 has not received therapeutical application because of its high serum binding which is probably related mainly to its very low solubility.

Since the structures of novobiocin and coumermycin A_1 have the partial structure (III) in common, it was conceivable that structures differing in the R and R' substituents may have useful antibiotic properties and thus the total syntheses of such compounds merited investigation.



III

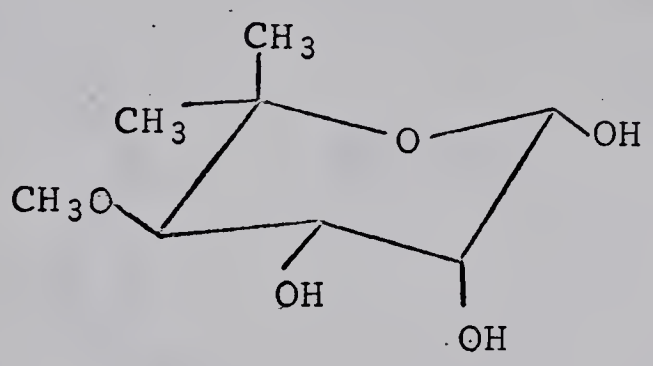
The coumarin aglycon is readily available (13, 14). Kaczka and co-workers (15) have shown that when the double

bond of the 3-methyl-2-butenyl group of novobiocin was reduced by catalytic hydrogenation, yielding dihydronovobiocin, it lost no biological activity. Other investigations (16) have indeed shown that the antibiotic properties of coumermycin A_2, are much inferior than that of coumermycin A_1; that is, when the methyl group of O-5-methyl-2-pyrrolecarbonyl residue of (II) is replaced by hydrogen, the biological activity is reduced. Thus, syntheses in the general area of these antibiotic structures appeared of interest not only from the point of view of developing antibiotics of improved therapeutical values but also perhaps to aid in studies of the relationship of structure to activity.

The general mode of action of the antibiotic novobiocin is that it inhibits growth by forming specific complexes with magnesium ions (17). Since a wide variety of enzyme and cell functions require magnesium ions for activity, a magnesium deficiency can have profound influences on the functioning of a cell. It is of interest to consider the reason for the selective toxicity of the antibiotic. As Webb (18) has shown, Gram-positive organisms have a ten-fold higher requirement for magnesium than Gram-negative organisms. Novobiocin is more active against Gram-positive than Gram-negative organisms although certain Gram-negative bacteria, i.e. Proteus and Klebsiella are fairly sensitive. Since all organisms presumably require magnesium, and since there seems to be no selective binding of novobiocin to antibiotic-sensitive cells, it seems likely that novobiocin

would inhibit growth of all organisms to degrees parallel with their magnesium requirements.

The main requirement for the syntheses of structures of type (III) which are analogous of novobiocin and coumermycin is a source of the 7-carbon branched-chain sugar (IV) designated by the trivial name noviose (19). Noviose has been isolated from hydrolyzates of these



β-Noviose

(IV)

antibiotics (12, 19) as a crystalline substance, m.p. 128-130°, $[\alpha]_D$ + 24° in low yields. As seen from structure (IV), the systematic name is 6-deoxy-5-C-methyl-4-O-methyl-β-L-lyxo-hexopyranose.

The purpose of the present research was to provide an improved synthesis of this sugar. Vaterlaus, Kiss and Spiegelberg (20) synthesized noviose from D-glucose by utilizing 3,5,6-tri-O-benzyl-2-O-methyl-D-galactono-1,4-lactone as their key intermediate. The synthetic sequence is given in Fig. 1.

Fig. 1. Synthesis of noviose from D-glucose (R = benzyl).

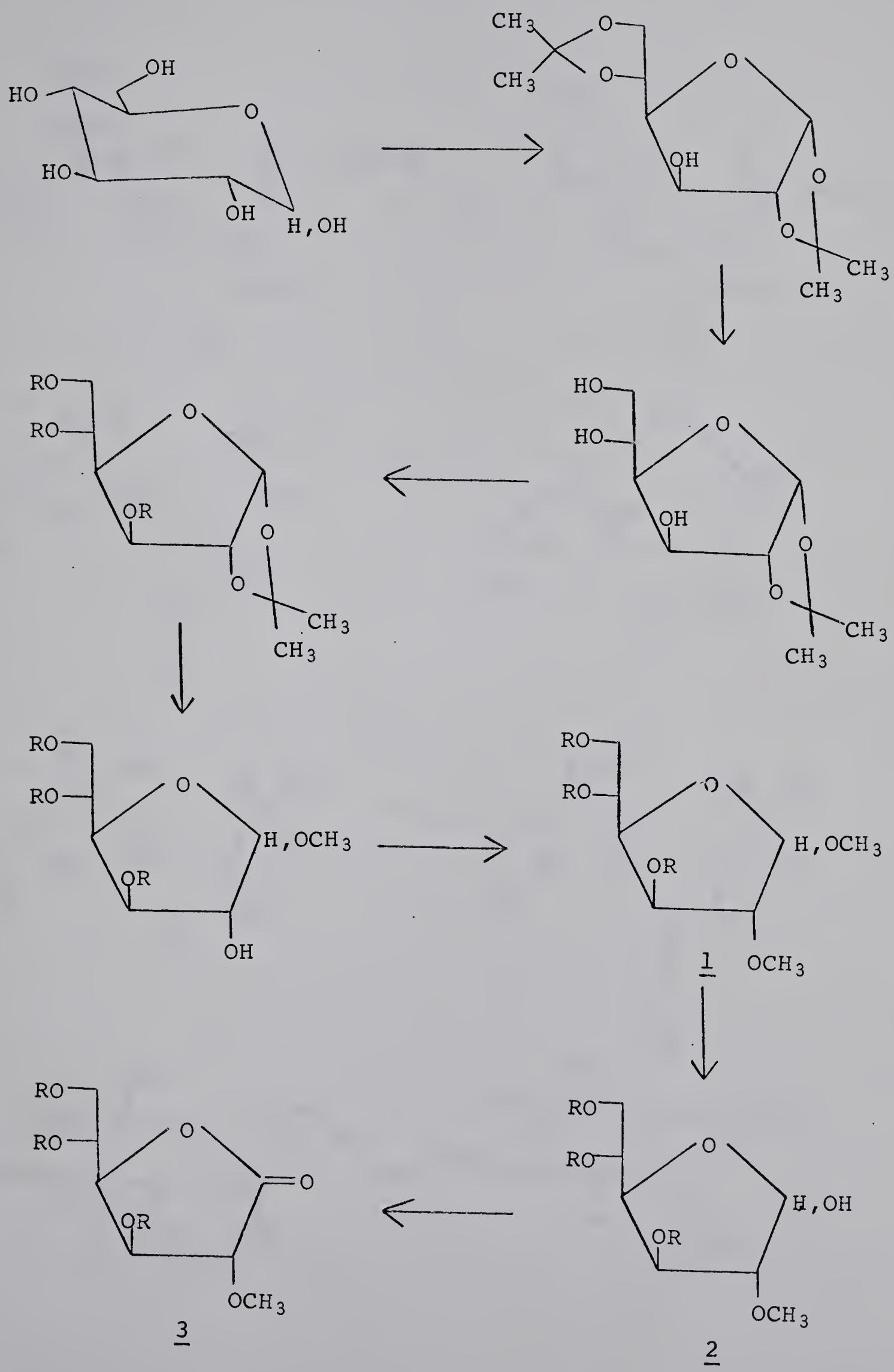
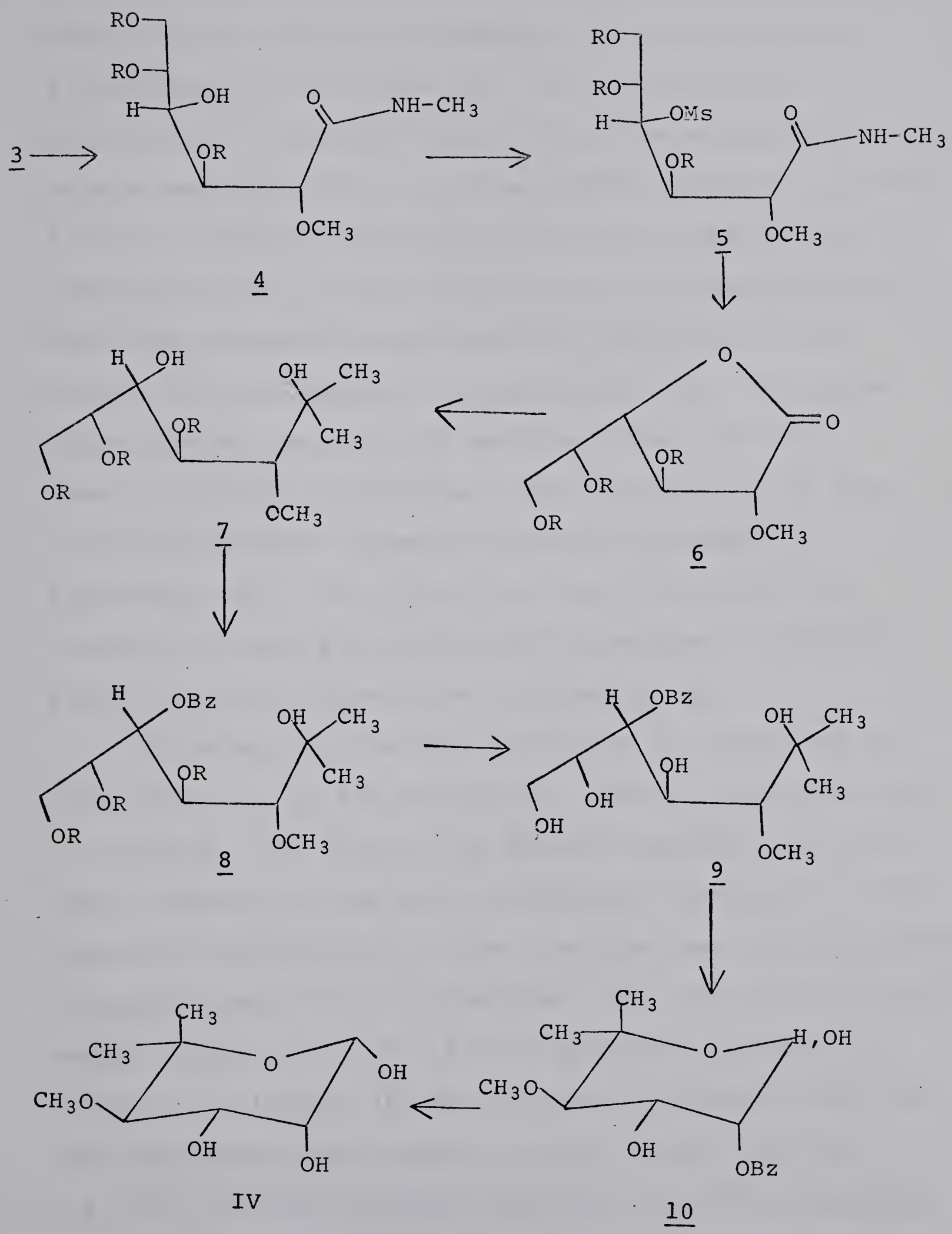


Fig. 1 (cont'd)


3
RO
RO
H
OH
OR
O
NH-CH3
OCH3
4
RO
RO
H
OMs
OR
O
NH-CH3
OCH3
5
O
O
OR
OR
OR
OCH3
6
H
OH
OR
OR
OR
OH
CH3
CH3
OCH3
7
H
OBz
OR
OR
OR
OH
CH3
CH3
OCH3
8
H
OBz
OH
OH
OH
OH
CH3
CH3
OCH3
9
CH3
CH3
O
H,OH
CH3O
OH
OBz
10
CH3
CH3
O
OH
CH3O
OH
OH
IV

Methyl 3,5,6-tri-O-benzyl-2-O-methyl-D-glucofuranosides (1) (21) were hydrolyzed with boiling 66% acetic acid to yield both anomers of 3,5,6-tri-O-benzyl-2-O-methyl-D-glucofuranose (2). The glucofuranose derivative was oxidized either with N-bromoacetamide or bromine and urea (22) in aqueous methanol solution to give 3,5,6-tri-O-benzyl-2-O-methyl-D-glucono-1,4-lactone (3) in comparable yield. The γ-lactone ring was opened by treatment with methanolic methylamine to yield 3,5,6-tri-O-benzyl-2-O-methyl-N-methyl-D-gluconamide (4). The amide derivative was reacted with methanesulfonyl chloride (mesyl chloride) in pyridine at room temperature to give 3,5,6-tri-O-benzyl-4-O-mesyl-2-O-methyl-N-methyl-D-gluconamide (5). The crystalline mesyl derivative was treated with warm 66% acetic acid to produce 3,5,6-tri-O-benzyl-2-O-methyl-D-galactono-1,4-lactone (6).

The galactono-γ-lactone derivative (6) exhibited an absorption band in the infrared at 1788 cm^{-1} indicative of a γ-lactone. The sign of the specific rotation, $[\alpha]_D$ -47°, was as expected on the basis of Hudson's lactone rule (23). Catalytic hydrogenation of the γ-lactone gave the crystalline 2-O-methyl-D-galactono-1,4-lactone. The introduction of two methyl groups on C-1 of 3,5,6-tri-O-benzyl-2-O-methyl-D-glactono-1,4-lactone (6) was achieved by Grignard reaction with methylmagnesium bromide in ether-benzene solution. 4,6,7-Tri-O-benzyl-1-deoxy-2-C-methyl-3-O-methyl-D-galacto-heptitol (7) was preferentially benzoylated with benzoyl

chloride in pyridine to give the 5-O-benzoyl derivative (8) which was hydrogenated over palladium black in methanol to yield 5-O-benzoyl-1-deoxy-2-C-methyl-3-O-methyl-D-galacto-heptitol (9). Oxidation of the tetraol with lead tetraacetate in methylene chloride afforded 2-O-benzoylnoviose (10). The benzoyl group was removed by treatment with alkali in aqueous methanolic solution to give noviose (IV). This synthesis involves fifteen steps from D-glucose and the overall yield from the intermediate methyl 3,5,6-tri-O-benzyl-2-O-methyl-D-glucofuranosides in ten steps was approximately 6%.

Vaterlaus and co-workers also succeeded in the synthesis of novobiocin (24) from 2,3-O-carbonyl-β-noviosyl chloride (25). The synthesis is given in Fig. 2.

The glycosidation of 4-benzyloxy-7-hydroxy-8-methyl-coumarin (1) (13, 14) with 2,3-O-carbonyl-β-noviosyl chloride (2) led to 4-benzyloxy-7-(2,3-O-carbonyl-α-noviosyloxy)-8-methyl-coumarin (3). The α-glycoside was hydrogenated over palladium black in ethyl acetate, and the product (4) was treated with the diazonium solution obtained from aniline and nitrous acid to give 7-(2,3-O-carbonyl-α-noviosyloxy)-4-hydroxy-8-methyl-3-phenylazo-coumarin (5). The phenylazo derivative was hydrogenated over palladium black in ethyl acetate to yield 3-amino-7-(2,3-O-carbonyl-α-noviosyloxy)-4-hydroxy-8-methyl-coumarin (6). Acylation of the latter compound with 4-acetoxy-3-(isopent-2'-enyl)-benzoyl chloride (14) gave 3-[4-acetoxy-3-(isopent-2'-enyl)-

Fig. 2. Synthesis of novobiocin (I).

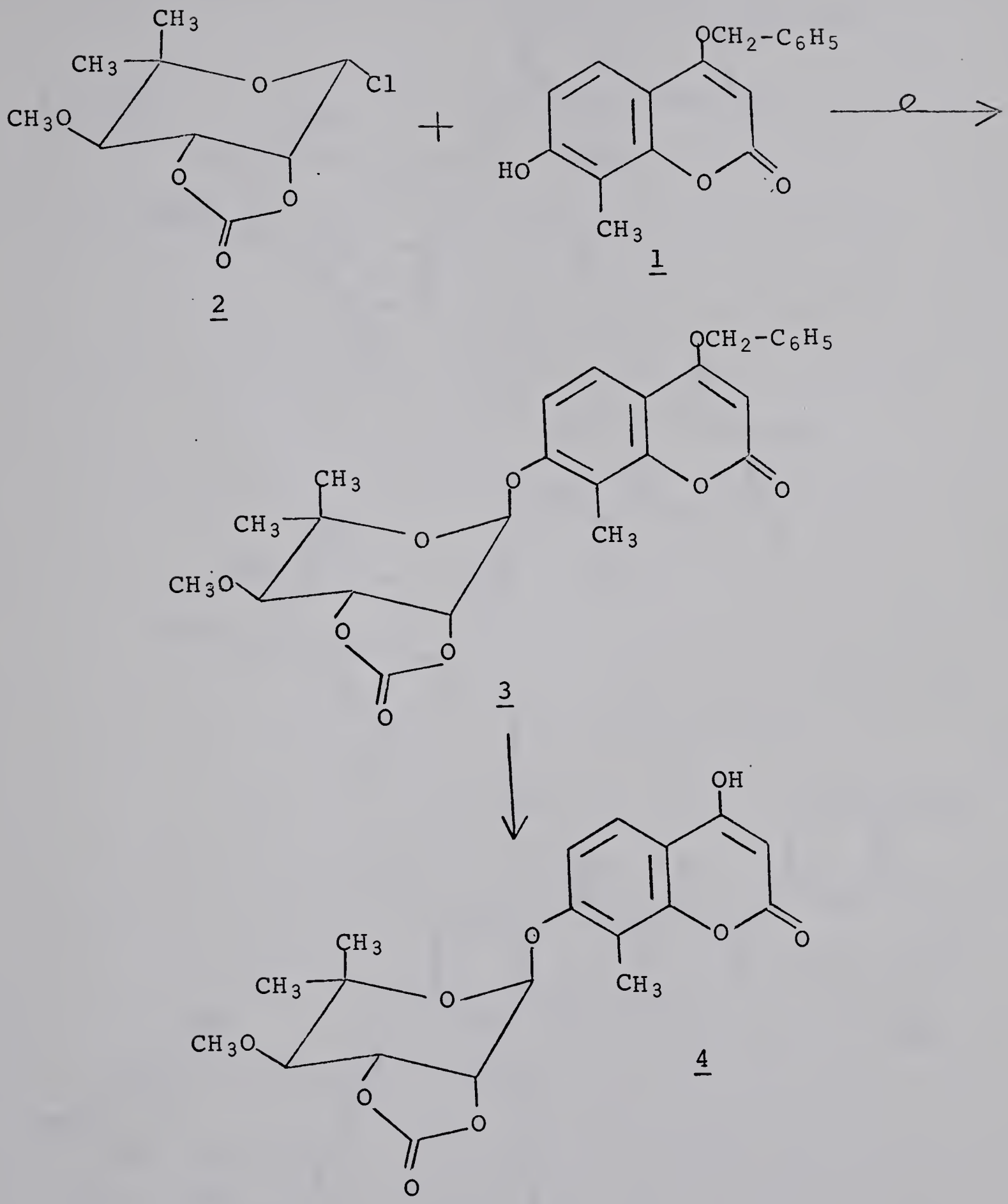
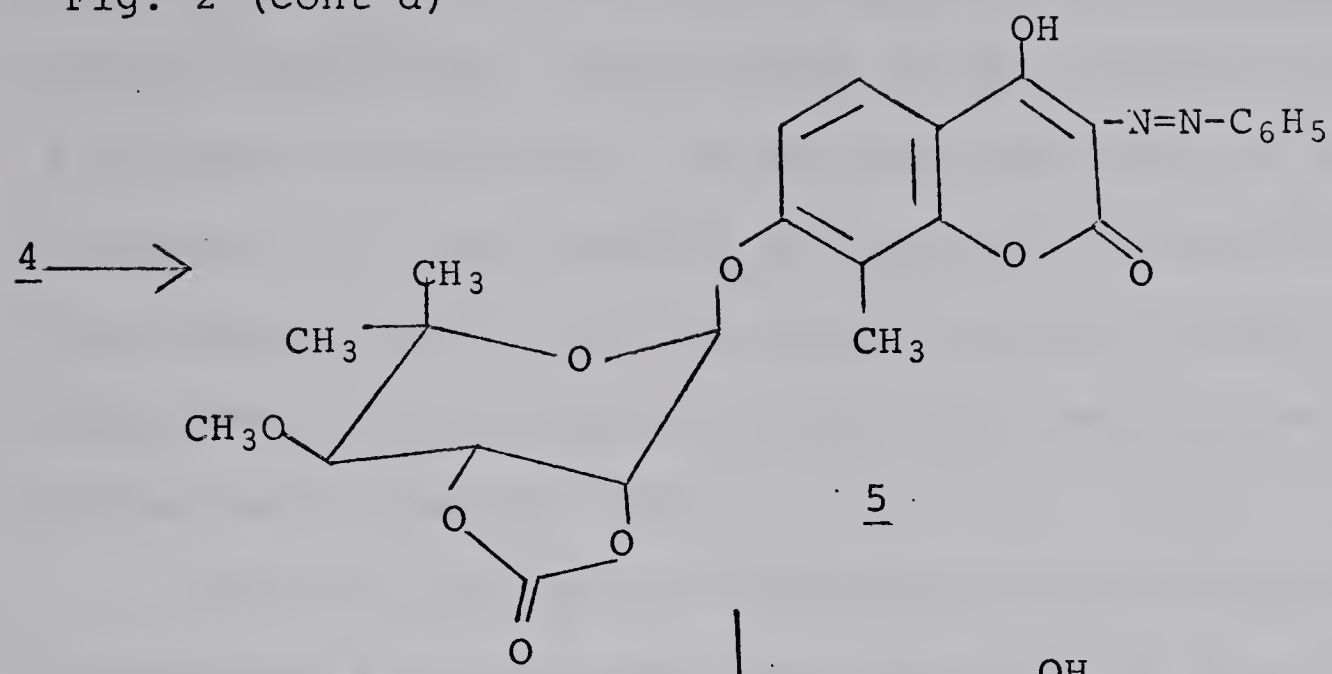
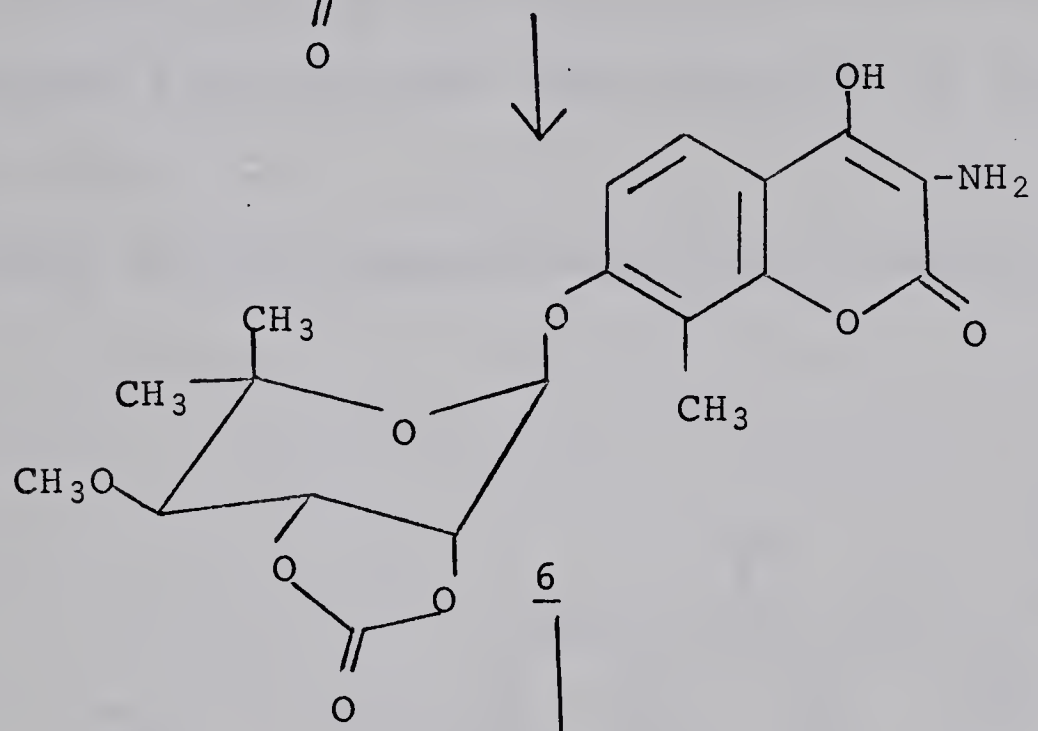
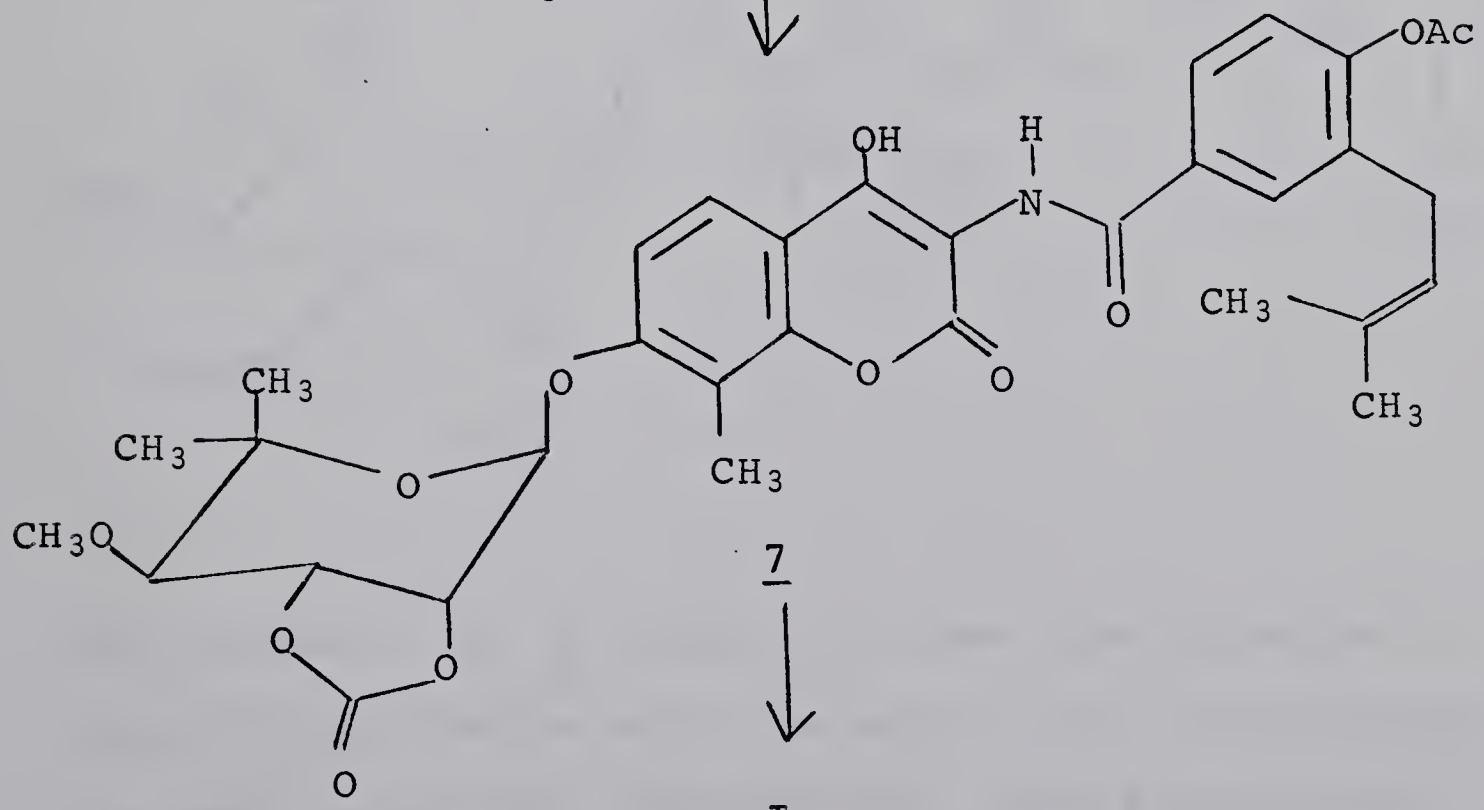


Fig. 2 (cont'd)


4
OH
-N=N-C6H5
CH3
CH3
CH3O
O
O
O
O
O
CH3
5

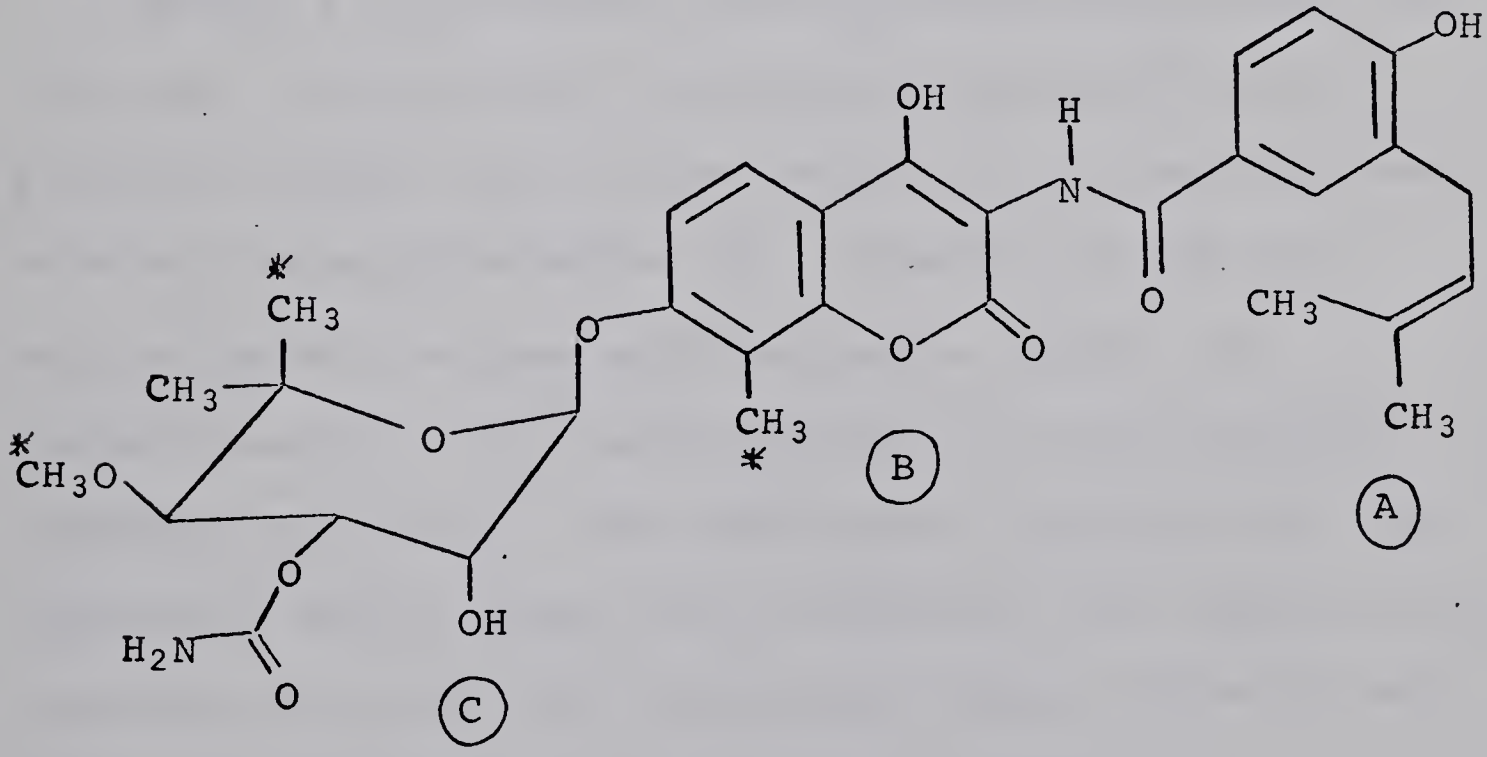

OH
-NH2
CH3
CH3
CH3O
O
O
O
O
O
O
CH3
6


OAc
OH
H
N
O
CH3
CH3
CH3
CH3O
O
O
O
O
O
O
O
7
I

benzamido]-7-(2,3-O-carbonyl-α-noviosyloxy)-4-hydroxy-8-methyl-coumarin (7) Ammonolysis of the product afforded a mixture of novobiocin (I) and isonovobiocin, of which novobiocin (I) was obtained by fractional crystallization. Isonovobiocin which has the carbamoyl group at the 2-position of the noviose residue, was found to be biologically inactive (26).

It is of interest to note that epi-noviose was also synthesized from D-glucose and epimerized by alkali to noviose (27).

Birch (28) has demonstrated that, in nature, the



amino-coumarin (B) of novobiocin comes from tyrosine by oxidative cyclization with the methyl group being derived from methionine (29). The acid (A) comes from tyrosine and the side-chain is an isoprene unit. The sugar (C) is

directly derived from D-glucose without fragmentation (30). The methyl groups marked with asterisk are derived from methionine (29). The acylamino-coumarin is built up, possibly with the insertion of the methyl group as the next stage. This is followed by the formation of the glycosidic linkage. Acids related to (A) containing p-OCH_3 or NH_2 groups usually give analogous compounds which have no, or much reduced activity.

Walton and co-workers (31), in their proof of the structure of noviose, synthesized 2,3-O-isopropylidene-5-O-methylnovionic acid from methyl 2,3-O-isopropylidene-L-rhamnofuranosides. The synthetic scheme is given in Fig. 3.

Methyl 2,3-O-isopropylidene-L-rhamnofuranosides (1) (32) were oxidized with the neutral chromium trioxide-pyridine complex (33) to give methyl 2,3-O-isopropylidene-5-keto-L-rhamnofuranosides (2). Reaction of the keto derivative with excess methylmagnesium iodide (34) produced methyl 2,3-O-isopropylidene-5,5-di-C-methyl-L-lyxofuranosides (3). The substituent isopropylidene and glycosidic methyl groups were removed by mild aqueous acid hydrolysis to yield the intermediate aldose (4) which was oxidized with bromine in neutral solution to give 5,5-di-C-methyl-L-lyxono-1,4-lactone (5). The γ-lactone derivative was converted into its crystalline 2,3-O-isopropylidene derivative (6) using hydrogen chloride as catalyst. The isopropylidene lactone was hydrolyzed rapidly

Fig. 3. Preparation of 2,3-O-isopropylidene-5-O-methylnovionic acid.

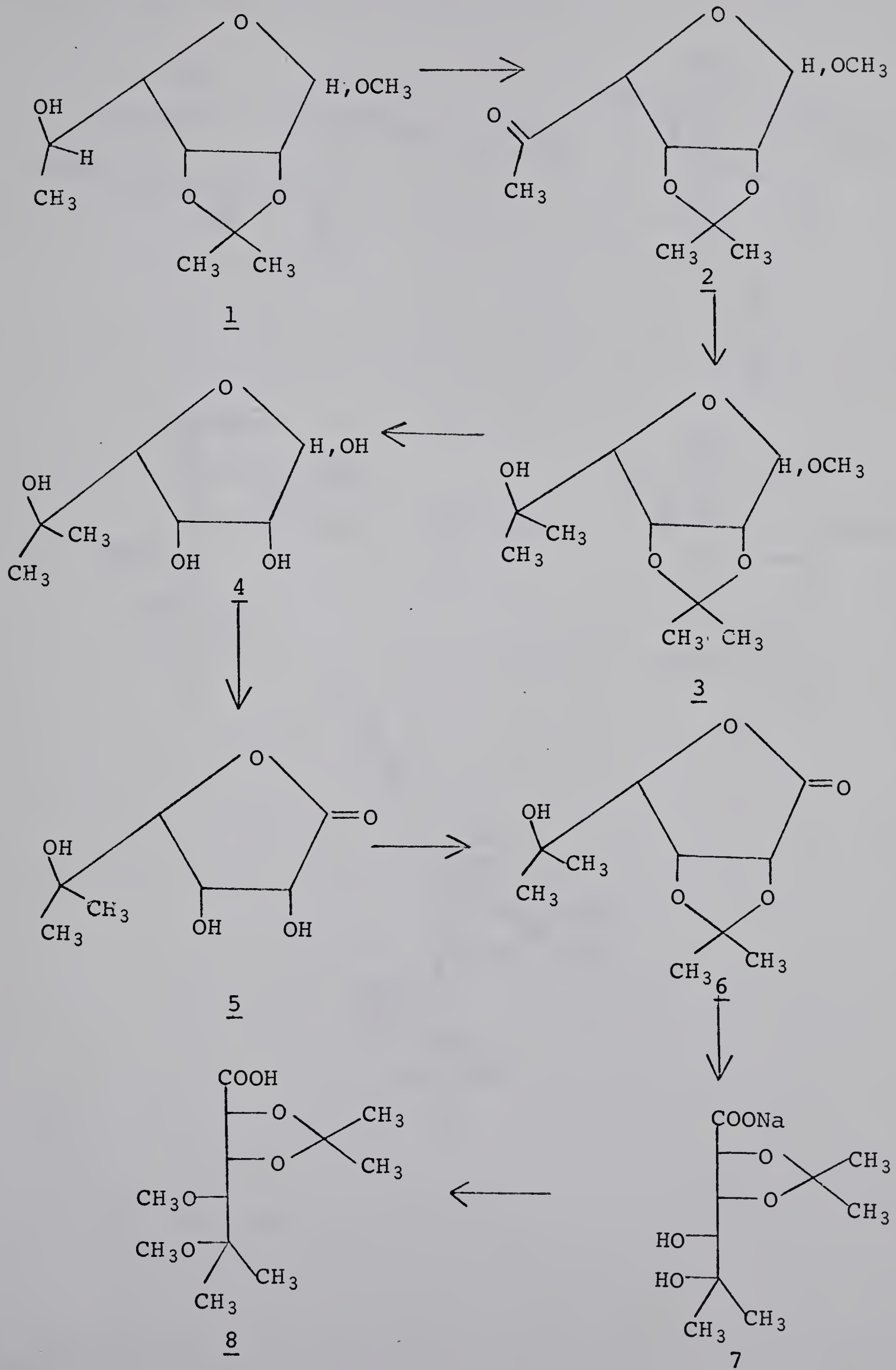
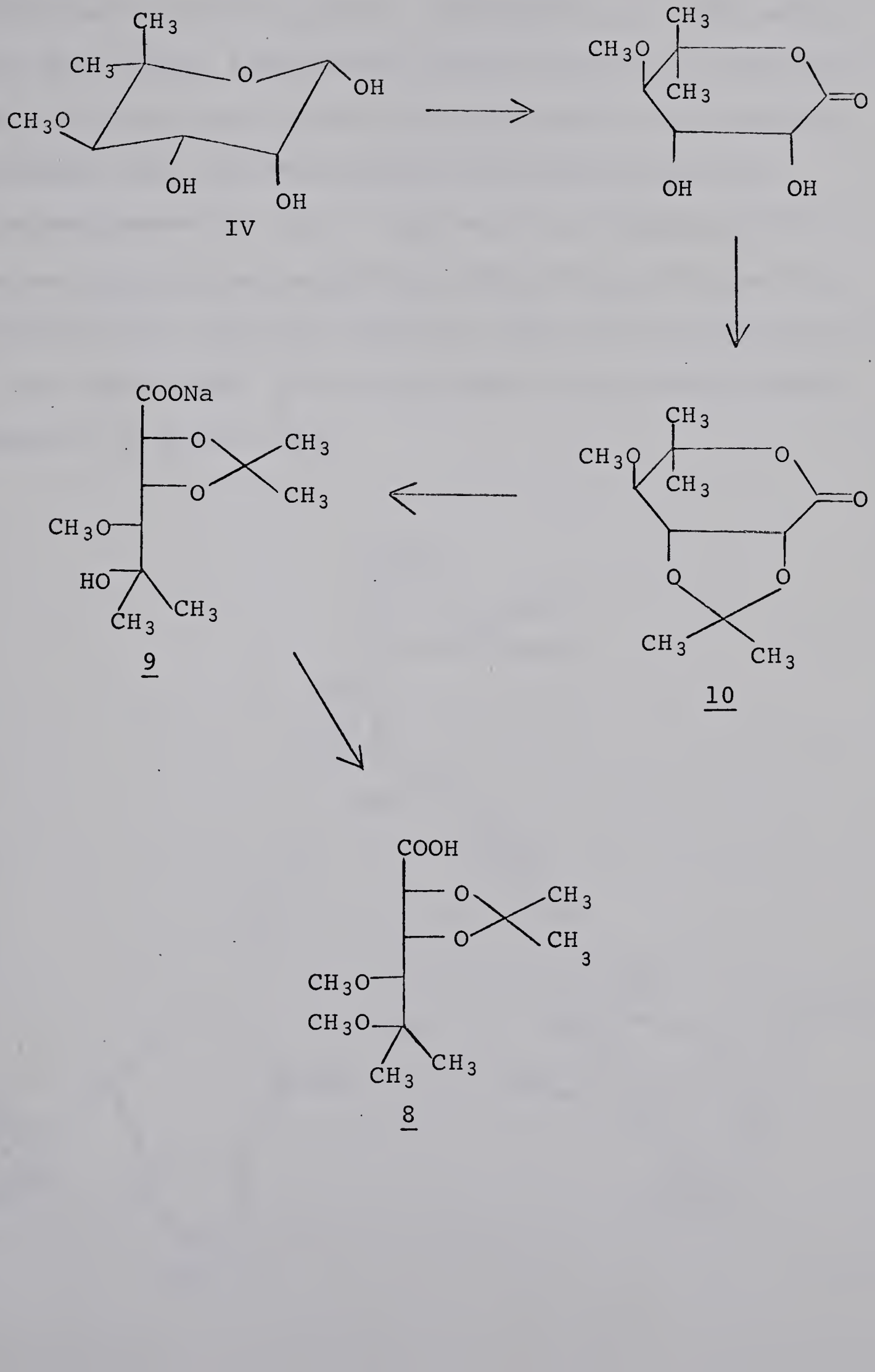
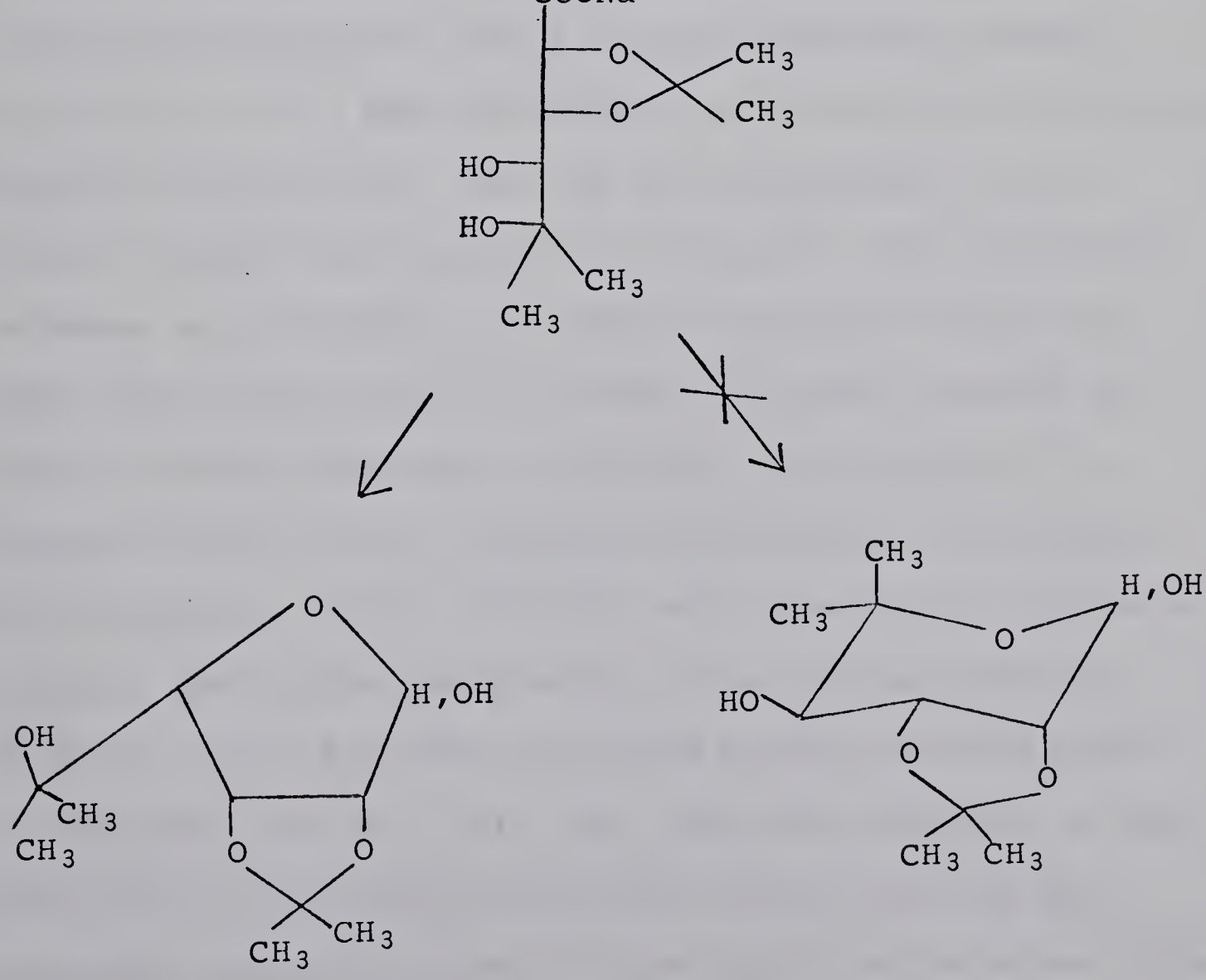


Fig. 3 (cont'd)


CH3
CH3
O
OH
CH3O
OH
OH
IV
CH3
CH3O
O
CH3
O
OH
OH
CH3
CH3O
O
CH3
O
O
O
CH3
CH3
COONa
O
CH3
O
CH3
CH3O
HO
CH3
CH3
9
10
COOH
O
CH3
O
CH3
CH3O
CH3O
CH3
CH3
8

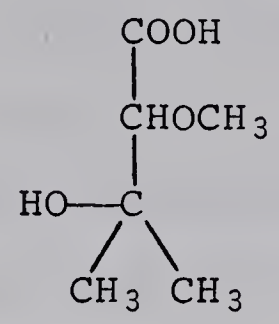
with one equivalent of aqueous sodium hydroxide and lyophilization of this solution gave the corresponding sodium salt (7) as a powder. Dimethylation of the sodium salt with methyl iodide was accomplished in low yield (35). The 2,3-O-isopropylidene-5,5-di-C-methyl-4,5-di-O-methyl-L-lyxonic acid (8) was isolated and purified as its benzhydrylammonium salt. This salt was identical with the benzhydrylammonium salt of 2,3-O-isopropylidene-5-O-methylnovionic acid (8) which was obtained by monomethylation of the sodium salt (9) derived from 2,3-O-isopropylidene-noviono-1,5-lactone (10).



In this laboratory, the properties of the de-O-methylnoviose obtained from sodium 2,3-O-isopropylidene-5,5-di-C-methyl-L-lyxonate were examined (36). As would be expected from the conformational analysis, the compound existed almost entirely in the furanose form since the pyranose form is strongly destabilized by the presence of an axial methyl group. In contrast, rhamnose (36) exists nearly entirely in the pyranose form. Evidently, therefore, any synthesis of noviose requires that the 4-O-methyl group be introduced prior to the liberation of the lactol ring.

Location of the carbamoyl group at the 3-position was proved as follows: Novobiocin, as mentioned, is a crystalline antibiotic which has the molecular formula $C_{31}H_{36}N_2O_{11}$ (4). When novobiocin is cleaved with methanolic hydrogen chloride (7, 15), one of the products is the neutral crystalline glycoside, $C_{10}H_{19}NO_6$. This glycoside consumes no periodate, but, after hydrolysis to the free sugar with dilute acid, the latter consumes one mole per mole of sodium periodate, indicating the presence of a hydroxyl group at C-2. Alkaline hydrolysis of $C_{10}H_{19}NO_6$ yields ammonia, carbon dioxide, and a new methyl glycoside, $C_9H_{18}O_5$, confirming the presence of a urethan grouping, $-O-\overset{O}{\overset{\|}{C}}-NH_2$, which had been indicated by the infrared bands at 1702 and 1625 cm^{-1} (4). The tentative location of this group at C-3 was verified by the finding that the new glycoside consumes one mole of periodate per mole and affords

glyoxal after hydrolysis with mild acid. The remainder of the molecule was identified, after bromine oxidation, as (-)-3-hydroxy-2-methoxy-3-methyl butanoic acid (V).



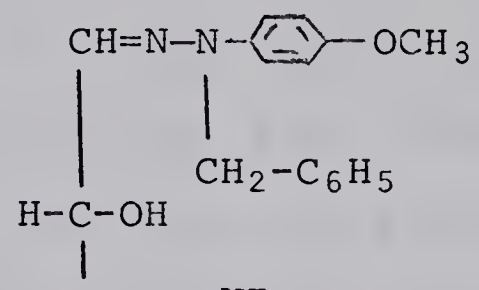
(-)-3-Hydroxy-2-methoxy-3-methylbutanoic acid

(V)

Boiling methanolic hydrogen chloride caused elimination of the nitrogen atom as ammonium chloride from the neutral glycoside $C_{10}H_{19}NO_6$. Another neutral substance, $C_{10}H_{16}O_6$, was formed which had an infrared absorption spectrum and chemical properties indicative of a cyclic carbonate ester (19). Reaction of this product with barium hydroxide gave barium carbonate and the methyl glycoside, $C_9H_{18}O_5$, which had been obtained directly by alkaline hydrolysis. Chromic acid oxidation (8) of the methyl glycoside gave acetone, isolated in 46% yield as the 2,4-dinitrophenylhydrazone. This confirmed the presence of gem-dimethyl groups indicated by the twin infrared bands at 1382 and 1366 cm^{-1} (4). The n.m.r. spectrum (37) indicated the presence of a methoxyl group, in addition to the glycosidic methoxyl group. This confirmed the expectation based on the elemental analysis (19).

The configuration at the various carbon atoms has been determined by Walton and co-workers (31, 38). This will be described briefly as follows:

Hydrolysis of the methyl glycoside, $C_9H_{18}O_5$, with 0.1 N hydrochloric acid followed by reaction with N^2-benzyl-N^2-(p-methoxyphenyl)hydrazine yielded the N^2-benzyl-N^2-(p-methoxyphenyl)hydrazone of the aldose (VI) which had $[\alpha]_D^{28}$-41° in methanol. This negative optical rotation permitted assignment of the C-2-hydroxyl group to

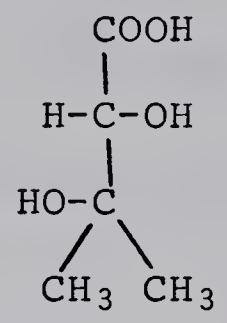


VI

the right in the Fischer projection, in the light of Votoček's work (39) which showed that N^2-benzyl-N^2-phenylhydrazones of aldoses having the C-2-hydroxyl on the right have negative rotations at the sodium D-line.

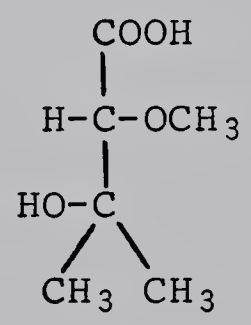
The observation (4, 8, 19) that a cyclic carbonate ester involving the C-2 and C-3-hydroxyl groups is formed indicated that these groups are likely to be cis. Although this may not be true since some trans cyclic carbonates on pyranose rings are recently known (147), the n.m.r. spectrum of methyl α-novioside (44) (see Table II) indicates that the C-2 and C-3 hydroxyl groups are indeed cis. During the degradation, (-)-3-hydroxy-2-methoxy-3-methylbutanoic acid (V) was obtained (7). Its enantiomorph,

(+)-3-hydroxy-2-methoxy-3-methylbutanoic acid was synthesized (7) from (-)-2,3-dihydroxy-3-methylbutanoic acid (VII) (40).



VII

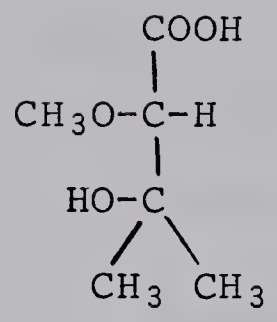
The rotation of the dihydroxy acid (VII) in 1N hydrochloric acid is $[\alpha]_D^{25}$ -14.7° (C, 1.64); in 1N sodium hydroxide, $[\alpha]_D^{30}$ +4.8° (C, 1.8). This positive shift in rotation in going from the acid to its ion is characteristic of D-α-hydroxy acids having one asymmetric center (41). Since the C-2-hydroxyl group in the dihydroxy acid (VII) is on the right in the Fischer projection, (+)-3-hydroxy-2-methoxy-3-methylbutanoic acid must have the structure VIII .



(+)-3-Hydroxy-2-methoxy-3-methylbutanoic acid

(VIII)

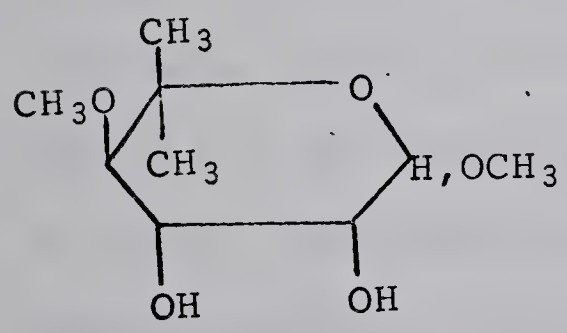
Therefore, the stereochemistry of (-)-3-hydroxy-2-methoxy-3-methylbutanoic acid must be Va .



(-)-3-Hydroxy-2-methoxy-3-methylbutanoic acid

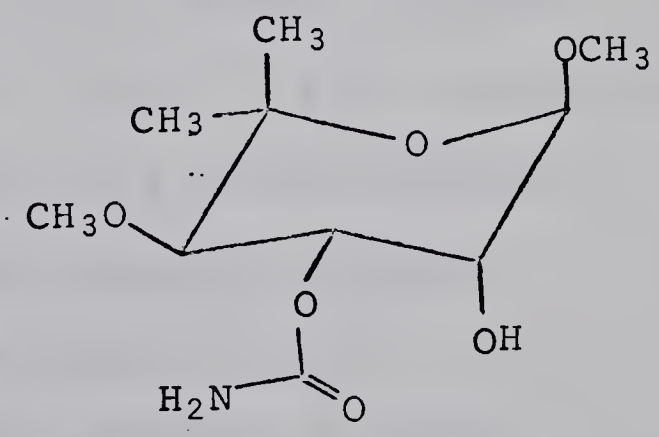
(Va)

Since C-2 in the methoxy acid (Va) corresponds to C-4 in the methyl glycoside, $C_9H_{18}O_5$, then the C-4 methoxyl in this compound must also be on the left. Hence, the configuration is L-lyxo, and the systematic name for the methyl glycoside, $C_9H_{18}O_5$, is methyl 6-deoxy-5-C-methyl-4-O-methyl-L-lyxo-hexopyranoside (IX) which is also known as methyl novioside.



Methyl novioside

(IX)



Methyl 3-O-carbamoyl-α-novioside

(X)

Various novioside derivatives in solution all have been shown to exist in the 1C conformation (42). For example, the n.m.r. parameters of methyl 3-O-carbamoyl-α-novioside (X) in pyridine is given in Table I (42).

Table I

N.m.r. parameters of methyl 3-O-carbamoyl-α-novioside in pyridine

Chemical shifts (τ values)					
H-1	H-2	H-3	H-4	1-OCH_3	4-OCH_3
4.97	5.32	4.20	6.02	6.61	6.43

Coupling constants (Hz)		
$J_{1,2}$	$J_{2,3}$	$J_{3,4}$
2.3	3.0	10.0

The H-4 signal of X at τ6.02 is a doublet due to strong spin-coupling with the adjacent H-3 ($J_{3,4}$ = 10.0 Hz), indicating that both H-4 and H-3 are axial. The H-3 resonance at τ4.20 is the expected quartet in which the diaxial coupling of H-3 and H-4 is again evident together with weak coupling to H-2 ($J_{2,3}$ = 3.0 Hz). H-2 is, therefore, cis to H-3 and equatorial, absorbing as a narrow multiplet at τ5.32. The doublet at τ4.97 is the anomeric hydrogen weakly coupled to its equatorial neighbour ($J_{1,2}$ = 2.3 Hz). These data are consistent only with existence of methyl 3-O-carbamoyl-α-novioside in the 1C conformation (X).

The pyranose ring of novobiocin itself also exists in the 1C conformation in pyridine (42). The sugar derivative is attached glycosidically to the C-7 hydroxyl group of 3-[4-hydroxy-3-(3-methyl-2-butenyl)benzamido]-4,7-dihydroxy-8-methylcoumarin. Based on Hudson's rules of isorotation (43),

novobiocin is found to be an α-novioside (37). The complete stereochemistry of novobiocin is represented in structure I .

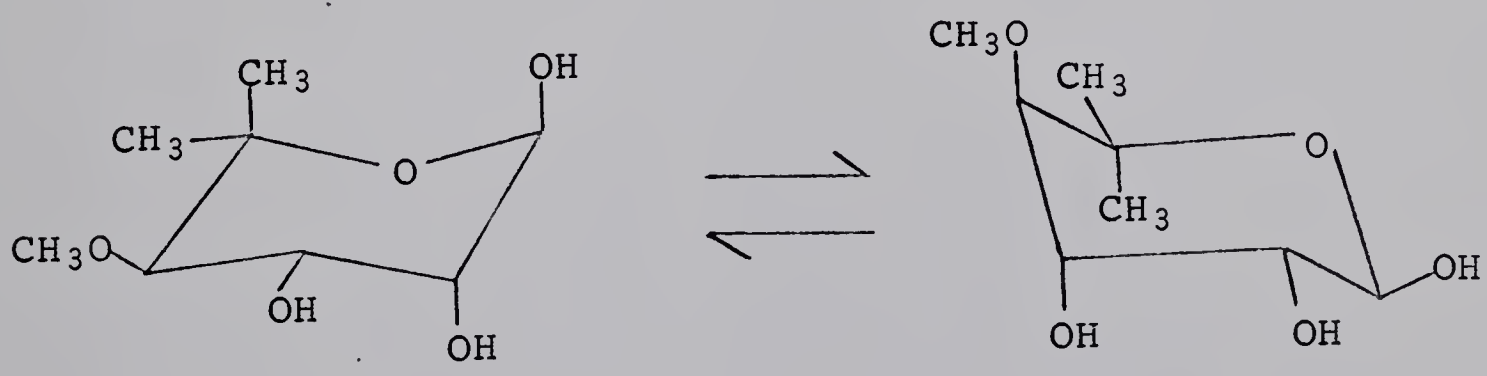
Noviose is known in one crystalline form which has been found to be the β-anomer (IV) (44). Its rotation decreases during mutarotation. In pyridine solution, in which mutarotation is slow, the initial n.m.r. spectrum shows only one anomeric proton (τ4.74, that of the β-form); another signal appears gradually at τ4.23, and is assigned to the anomeric proton of the α-anomer. This is in agreement with the observations of Lemieux and co-workers (45) which indicate that axially oriented protons are more shielded than their equatorial counterparts. In aqueous solution, the n.m.r. spectrum (44) shows that the α- and β-anomers are present in the ratio 26:74 (±2). The relevant n.m.r. data is given in Table II (44).

Table II

N.m.r. parameters of α- and β-noviose and methyl α-novioside. Chemical shifts (τ) and coupling constants (Hz) in deuterium oxide

	H-1	H-4	CH_3	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$
methyl α-novioside	5.35	6.70	8.72,8.64	2.3	3.4	8.8
α-noviose	4.94	6.70	8.72,8.64	3.9	3.4	7.7
β-noviose	5.04	6.78	8.83,8.67	1.0	3.3	9.5

The coupling constants indicate that, in aqueous solution, α-noviose represents a conformational mixture: $J_{1,2}$ is considerably larger, and $J_{3,4}$ considerably smaller, than in methyl α-novioside. The n.m.r. spectra of several derivatives of methyl α-novioside in pyridine solution have been published (42) and, in all cases, $J_{1,2} \leq 2.3$ and $J_{3,4} \geq 9.3$ Hz. The large coupling of H-3 and H-4 clearly indicates that they are both axial; both the α- and β-noviosides are in the 1C conformation as mentioned before. Thus, the coupling constants of α-noviose in aqueous solution must represent the weighted averages of two conformations. Summation of the interaction energies (44) indicates that the C1 conformation (IVα') is only slightly less stable than the 1C conformation (IVα). Angyal (44) has calculated that the 1C conformation (IVα) exists to an



IVα ⇌ IVα'

extent of approximately 70%.

Methyl α-novioside and its derivatives do not exist as conformational mixtures in pyridine solution (42) because

the anomeric effect of a methoxyl group is greater than that of a hydroxyl group, and the effect is greater in pyridine than in water (46). However, in aqueous solution, methyl α-novioside exists partially in the C1 conformation, as judged by the value of $J_{3,4}$ (8.8 Hz).

A list of known derivatives of noviose is given in Table III.

Table III

Known derivatives of noviose

Compound	Melting Point, °C	Rotation	References
1,2-di-O-benzoyl-3-O-(p-nitrophenoxycarbonyl)-α-noviose	148-149	$[\alpha]_D^{25}$+65° (c, 1% in chloroform)	(25)
2-O-benzoyl-3-O-(p-nitrophenoxycarbonyl)-β-noviose	158-160	$[\alpha]_D$ +233° (c, 0.1% in dioxan)	(25)
2-O-benzoyl-3-O-(p-nitrophenoxycarbonyl)-α-noviosyl bromide	131-132	$[\alpha]_D$ +11.7 (c, 0.1% in dioxan)	(25)
2-O-benzoyl-3-O-(p-nitrophenoxycarbonyl)-α-noviosyl chloride	143-144	$[\alpha]_D$ +52.7° (c, 0.1% in dioxan)	(25)
2-O-benzoyl-3-O-(p-nitrophenoxycarbonyl)-α-noviosyl fluoride	156-158	$[\alpha]_D^{25}$ +184° (c, 1% in methylene chloride	(25)
2-O-benzoylnoviose	-	$[\alpha]_D^{22}$ +66.5° (c, 4% in chloroform)	(20)

Table III cont'd

Compound	Melting Point, °C	Rotation	References
3-O-carbamoylnoviose	124-126	-	(7,8)
2,3-O-carbonylnoviose	127-128	$[\alpha]_D^{25}$ +42° (c, 1% in methylene chloride).	(25)
2,3-O-carbonyl-β-noviosyl chloride	unstable oil	$[\alpha]_D^{25}$ +87° (c, 1% in nitromethane-acetyl chloride, 9:1	(25)
2,3-O-carbonyl-α-noviosyl trimethyl-ammonium chloride	187-188	$[\alpha]_D^{25}$ +7.5° (c, 1% in methanol)	(25)
1-deoxy-3-O-carbamoyl-noviose	117-118	-	(7)
1,1-diethyl dithiol-3-O-carbamoylnoviose	143-145	-	(7)
epi-noviose	79-82	$[\alpha]_D^{20}$ +21.6° (c, 0.2 in 50% alcohol)	(27)
ethyl 3-O-carbamoyl-novioside	173-175	$[\alpha]_D^{25}$ -36° (c, 1.0 in ethanol)	(19)

Table III cont'd

Compound	Melting Point, °C	Rotation	References
2,3-O-isopropylidene noviono-δ-lactone	100-102	$[\alpha]_D^{25}$ -41° (c, 1.8% in acetone)	(31)
methyl 2-O-acetyl-3-O-carbamoylnovioside	44-48	$[\alpha]_D^{24}$-14.0° (c, 1.136 in 95% ethanol)	(19)
methyl 2,3-di-O-acetylnovioside	62-64	$[\alpha]_D^{24}$ -20.4° (c,0.973 in 95% ethanol)	(19)
methyl 2-O-benzoyl-novioside	-	$[\alpha]_D^{22}$ +52-57° (c, 1% in ethanol)	(20)
methyl 2-O-benzoyl-α-novioside	102-103	$[\alpha]_D$ +13.6° (c, 0.103% in dioxan)	(20)
methyl 2-O-benzoyl-3-O-carbamoyl-α-novioside	-	$[\alpha]_D^{20}$ +45° (c, 1% in 95% ethanol)	(20)
methyl 2-O-benzoyl-3-O-(p-nitrophenoxy-carbonyl)-α-novioside	148-149	$[\alpha]_D$ +140° (c, 0.10% in dioxan)	(20)

Table III cont'd

Compound	Melting Point, °C	Rotation	References
methyl 3-O-carbamoyl-2-O-mesylnovioside	149-151	-	(19)
methyl 2-O-carbamoyl-α-novioside	208-211	$[\alpha]_D^{20}$ -9.9° (c, 1.0 in methanol)	(37)
methyl 3-O-carbamoyl-α-novioside	191-192	$[\alpha]_D^{25}$ -28° (c, 1.0 in methanol)	(7,8,20,37)
methyl 3-O-carbamoyl-β-novioside	155-157	$[\alpha]_D^{26}$ +130° (c, 1.0 in methanol)	(8,37)
methyl 2,3-di-O-carbamoylnovioside	132-132.5	$[\alpha]_D^{25}$ +117.7° (c, 0.998 in 95% ethanol)	(8,19)
methyl 2,3-O-carbamoylnovioside	$b_{0.05}$ 82-95	$[\alpha]_D^{25}$ -13° (c, 1% in ethanol)	(25)
methyl 2,3-O-isopropylidenenovioside	N_D^{25} 1.4438	$[\alpha]_D^{28}$ -13° (c, 1.36 in methanol)	(31)
methyl α-novioside	69-71	$[\alpha]_D^{25}$ -50° (c, 1.13 in water)	(7,8,19,37)

Table III cont'd

Compound	Melting Point, °C	Rotation	References
methyl β-novioside	66-67.5	$[\alpha]_D^{27}$ +106° (c, 0.7 in water)	(7,8,19,37)
noviono-δ-lactone	111-113	$[\alpha]_D^{25}$ -35° in 0.1N HCl (c, 1) +14° in 0.1N NaOH (c, 1)	(31)
β-noviose	129-130°	$[\alpha]_D^{25}$ +24° (c, 1.0 in ethyl acetate)	(8,19)
O-tolyl-2-O-benzoyl-3-O-(p-nitrophenoxy-carbonyl)-α-novioside	185	$[\alpha]_D^{25}$ +66° (c, 0.86% in chloroform)	(25)

EXPERIMENTAL

I. Physical Methods of Analysis

All melting points were taken on a Leitz micro heating stage Model 350 and are uncorrected. Rotations were measured using a Perkin-Elmer (Model 141) polarimeter. Polarimetric rate determinations were accomplished using a Rudolph Instruments Engineering Co. automatic recording spectropolarimeter (Model 260/655/850/810-614) equipped with a thermostated water-jacketed polarimeter tube.

The refractive indices were measured with a Bausch and Lamb Optical Co. constant temperature refractometer (Model 33-45-58).

Nuclear magnetic resonance (n.m.r.) spectra at 60 MHz were determined with a Varian A60 spectrometer in the solvents noted in the text. The 100 MHz spectra were recorded on a Varian HA 100 spectrometer. Chemical shifts are reported as tau (τ) values with tetramethylsilane (TMS) as internal standard. Double- and triple-resonance experiments were performed to confirm the assignments of signals and splittings, using a frequency sweep technique (47, 48).

The infrared spectra were performed on a Perkin-Elmer 421 grating spectrometer. Infrared spectra of oils were determined as liquid films on potassium bromide disks and solids either using potassium bromide pellets or in Nujol as stated in the text.

Preliminary examinations of water-soluble reaction products were performed chromatographically on thin-layer plates of Microcrystalline Cellulose (49) or on Whatman No. 1 papers. The chromatograms were developed with the lighter phase of n-butanol, ethanol and water mixture (5:1:4)(50). The components were detected by dipping the plates or papers first in a solution of silver nitrate prepared by adding 1 ml of saturated aqueous solution of silver nitrate to 200 ml of acetone and then adding just sufficient water to redissolve the precipitate. The plates or papers were then sprayed with a 0.5 N solution of sodium hydroxide prepared by dissolving 5 g sodium hydroxide in 7.5 ml water and diluting to 250 ml with ethanol (51). The chromatograms were washed with sodium thiosulfate solution after the spots had developed to their maximum intensity.

Chromatoplates of Silica Gel G(52-54) were used for preliminary examinations of chloroform-soluble reaction products. The chromatograms were developed with a mixture of ethyl acetate and chloroform in the ratio of 4:1 or other solvent developers as indicated in the text. The components were detected by spraying first with 1% vanillin in ethanol followed by 25% sulfuric acid and heating on a hot plate (55).

Preparative chromatography was carried out on columns of silicic acid (100 mesh) or Silica Gel G using dry columns technique, the fractions being collected by a

mechanical fraction collector. Individual fractions were examined by optical rotation and t.l.c. (thin-layer chromatography).

The elementary analyses, infrared spectra and nuclear magnetic resonance spectra were determined by the departmental service laboratories.

Solvents were evaporated on a rotatory evaporator under diminished pressure with a maximum bath temperature of 50°, unless otherwise stated.

II. Reagents, Solvents, and Standard Solutions

The solvents were commercially available, and when necessary, were dried using established procedures (56). The chloroform and methylene chloride (reagent grades) when used in preparative procedures, were purified by passing through a column of activated alumina (57). The methylene chloride was kept over molecular sieve 4A which was supplied by Linde Company, Union Carbide Corporation, U.S.A..

Unless otherwise stated in the text, the solutions in organic solvents were dried with anhydrous sodium sulfate.

The silica Gel G for thin-layer and preparative chromatography was that supplied by E. Merck, Darmstadt, Germany. The silicic acid (100 mesh) used for preparative column chromatography was that supplied by Mallinckrodt Chemical Works. U.S.A. Microcrystalline cellulose "Avicel" is a product of the American Viscose Co., Newark, Deleware.

The 1,2-dimethoxyethane was refluxed over calcium hydride for two days and then over lithium aluminum hydride

and distilled before use.

Metal Hydrides Incorporated, Beverly, Massachusetts, supplied the 52.6% suspension of sodium hydride in mineral oil. The oil was removed by washing the dispersion with anhydrous ether and the hydride obtained by filtration.

Ion exchange resin IRA-400 ($\overline{O}Ac$) was prepared by passing sodium acetate solution through a column of Amberlite IRA-400 ($C\overline{l}$) supplied by Mallinckrodt Chemical Works.

The anhydrous aluminum chloride was resublimed, and powdered with exclusion of moisture, just before use.

The tetraethylammonium chloride was recrystallized from acetonitrile and dried *in vacuo* over phosphorus pentoxide.

Commercial antimony pentachloride was used without purification.

Anhydrous *P*-toluenesulfonic acid was obtained as described by A.R. Morgan (57). The ether extract of the monohydrate was dried over several lots of fresh phosphorus pentoxide in succession and evaporated to a syrup *in vacuo*. The syrup was then dissolved in methylene chloride and was stored, sealed with a serum cap, in the cold. Samples were removed with a syringe and were titrated just before use against standard sodium hydroxide solution.

Nitromethane was distilled twice over phosphorus pentoxide. 1,2-Dichloroethane was distilled over calcium carbonate and calcium chloride. Any water present in

commercially available phenol was removed by azeotropic distillation with benzene *in vacuo* at 40°C.

III. Preparation of 1,6-anhydro-3,4-O-isopropylidene-β-D-galactose (XI)

1. From D-galactose

This compound was prepared according to the published procedure (58), except that 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide was prepared from D-glactose without isolation of the intermediate anomeric D-galactopyranose pentaacetates (59). Compound XI had m.p. 151-152° and $[\alpha]_D^{29}$ -72° (c, 1.56 in chloroform) [Literature (58), m.p. 151-152°, $[\alpha]_D^{19}$ -73° (c, 1.7 in chloroform)]. The n.m.r. spectrum is shown in Fig. 4 and the parameters are presented in Table IV.

2. From α-lactose monohydrate

The published procedure for pyrolysis of α-lactose monohydrate (60) was modified as follows: Three successive charges of 75, 65 and 60 g of α-lactose monohydrate were pyrolyzed in the apparatus shown in Fig. 5. Copper powder (10 g) was mixed with both the second and third charge to improve heat transfer through the decomposing lactose (61). A layer of glass wool was placed above each charge to reduce frothing. The receiving flask was cooled in an ice-water bath and the flask containing the charge was heated with two Bunsen burners with large luminous flames. The pyrolysis required about 60 min. The combined pyrolyzates were

dissolved in 300 ml of water, and the solution was filtered through a layer of 45 g of Darco G-60 charcoal on top of a layer of filter-aid and evaporated *in vacuo* to a thick syrup. Any water present in the syrup was removed by azeotropic distillation with benzene, and dried under high vacuum at 50° overnight.

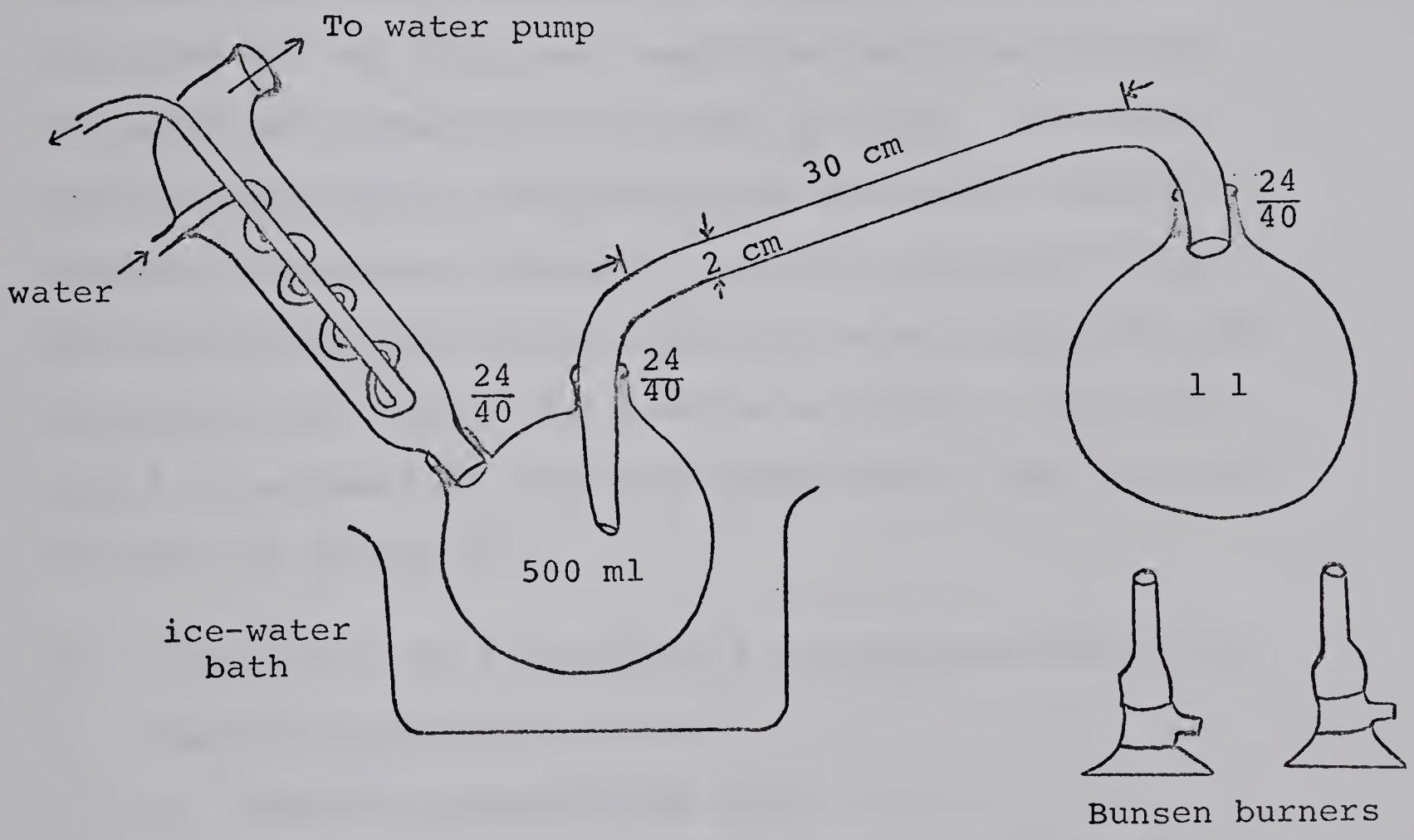


Fig. 5. Pyrolysis apparatus

p-Toluenesulfonic acid monohydrate (0.5 g) was dissolved in 2,2-dimethoxypropane (180 ml) and poured into a mixture of the dried syrup in N,N-dimethylformamide

(100 ml) (62-64). The reaction mixture was shaken until solution occurred and then allowed to stand at room temperature for 24 h. Triethylamine (5 ml) was added to the reaction mixture followed by a solution of potassium carbonate (20 g in 300 ml water). The flask was cooled with a stream of cold water and the product was extracted with chloroform (200, 100 and 2 x 50 ml successively). The combined chloroform extracts were washed with water (2 x 200 ml) and dried over anhydrous magnesium sulfate, filtered and evaporated to dryness in vacuo. The syrup crystallized and was recrystallized from ethyl acetate. Further quantities of material could be obtained through purification of the mother liquor by column chromatography on silicic acid with ethyl acetate as eluent. The total yield of compound XI (18%) was comparable to that reported by Hann and Hudson (60).

IV. Preparation of 1,6-anhydro-3,4-O-isopropylidene-2-O-methyl-β-D-galactose (XII)

1. Haworth's methylation (65).

In a 1-liter, three-necked flask equipped with a magnetic stirrer, condenser and two dropping funnels, 1,6-anhydro-3,4-O-isopropylidene-β-D-galactose (38 g) was dissolved in acetone (100 ml). Dimethyl sulfate (200 ml) and 30% sodium hydroxide (500 ml) in separate funnels were added gradually during 90 min at 50°. The temperature was then raised to 90° and the solution was refluxed for 10 min.

The reaction mixture was then allowed to cool, and extracted with chloroform (200, 2 x 100 ml). The combined chloroform extracts were washed with water (2 x 150 ml) and dried over anhydrous magnesium sulfate. By concentrating the filtered solution and drying under high vacuum at 60°, the title compound XII crystallized upon scratching. It was recrystallized from petroleum ether, yield 32.5 g (84%); m.p. 38-39°, $[\alpha]_D^{29}$ -85.5° (c, 1.77 in ethanol). The n.m.r. spectrum is shown in Fig. 7 and the parameters are presented in Table IV.

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46
Found: C, 55.52; H, 7.34%

1,6-Anhydro-3,4-O-isopropylidene-2-O-methyl-β-D-galactose (XII) was reported in the literature (66) as a syrup, b.p. (bath temp.) 110°/0.12 mm., N_D^{22} 1.4680, $[\alpha]_D^{17}$ -84.5° (c, 1.7 in ethanol).

2. Sodium hydride-methyl iodide procedure (67, 68)

In a 500-ml, three-necked flask equipped with a magnetic stirrer, condenser with a drying tube and a dropping funnel, compound XI (20 g, 0.099 mole) was dissolved in 1,2-dimethoxyethane (200 ml). Sodium hydride powder (4.8 g, 0.2 mole) was added and the suspension was stirred for 20 min before the addition, with cooling, of methyl iodide (18.5 ml, 0.297 mole). The reaction mixture was stirred at room temperature for 24 h. Methanol (50 ml) was added gradually to destroy the excess sodium

hydride. When effervescence had ceased, the solution was concentrated to dryness. The residue was partitioned between chloroform (500 ml) and water (500 ml), and the separated organic layer was washed with water (2 x 250 ml). It was dried over anhydrous magnesium sulfate, filtered and concentrated to dryness *in vacuo*. The product crystallized upon scratching, yield 21 g (98%). Recrystallization from petroleum ether afforded pure material, m.p. 38-39°. The melting point was undepressed in admixture with authentic 1,6-anhydro-3,4-O-isopropylidene-2-O-methyl-β-D-galactose (XII) obtained from dimethyl sulfate - sodium hydride procedure. The crude product appeared homogeneous (t.l.c.) and gave an n.m.r. spectrum identical to the purified material.

V. Acid hydrolysis of 1,6-anhydro-3,4-O-isopropylidene-2-O-methyl-β-D-galactose (XII)

In a 1-liter flask equipped with a condenser, 1,6-anhydro-3,4-O-isopropylidene-2-O-methyl-β-D-galactose (XII) (32.5 g) in 5% hydrochloric acid (800 ml) was refluxed on a steam bath for 21 h. The reaction mixture was cooled and then neutralized with lead carbonate. The filtered solution was treated with hydrogen sulfide and lead sulfide was removed by filtering through a packed Celite column. The clear solution was evaporated to dryness *in vacuo* and triturated a few times with 95% ethanol. 2-O-Methyl-β-D-galactopyranose (XIII) was crystallized from

glacial acetic acid, yield 24.8 g (85%). Recrystallization from 98% ethanol afforded pure material, m.p. 146-149°, $[\alpha]_D^{29}$ +52° → +95° (c, 1.60 in water). [Literature (66), m.p. 145-148°, $[\alpha]_D^{18}$ +52° → +94° (c, 0.5 in water)]. The n.m.r. spectrum is shown in Fig. 8 and the parameters are presented in Table V.

VI. Preparation of 2-O-methyl-D-galactono-1,4-lactone (XIV)

Bromine (11 ml, 0.206 mole) was added to an ice-cold solution of 2-O-methyl-β-D-galactopyranose (XIII) (36 g, 0.186 mole) and barium benzoate dihydrate (94 g, 0.226 mole) (69) in water (2 l). The mixture was shaken until the bromine dissolved, and the solution was stored in the dark at room temperature for 36 h. Excess bromine was removed with a stream of nitrogen; 5 N sulfuric acid (87 ml) was added, and the suspension was filtered. The filtrate was extracted with chloroform (3 x 200 ml) to remove dissolved benzoic acid, and the aqueous solution was stirred with silver carbonate (55 g). The insoluble salts were collected on a filter, washed with water, and discarded. To remove silver and barium ions, the bromine-free filtrate was passed through a column containing Amberlite IR-120 (H^+) (80 ml). The solution was filtered and evaporated to dryness *in vacuo* to yield the title compound XIV as a crystalline mass. The crude product was recrystallized from methylene chloride-ethyl acetate, yield 34.6 g (97%); m.p. 109.5-110°, $[\alpha]_D^{26}$ -62.8° → -26° after 224 h. (c, 1.6 in water);

IR: ν(CO) = 1788 cm^{-1}

Anal. Calcd. for $C_7H_{12}O_6$: C, 43.75; H, 6.29

Found: C, 43.48; H, 6.26%.

[Literature (20), m.p. 110-111°, $[\alpha]_D^{23}$ -63.5° → -56° after 64 h (c, 2% in water); IR: ν(CO) = 1788 cm^{-1}. Hirst and Jones (70) reported as a syrup, $[\alpha]_D^{20}$ -27° → -24° after 100 h and the value still rising (c, 1.5 in water)].

VII. Derivatives of 5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XV)

1. Preparation of compound XV

2,2-Dimethoxypropane (50 ml) was added to compound XIV (3.87 g) dissolved in 1,2-dimethoxyethane (50 ml) containing P-toluenesulfonic acid monohydrate (0.05 g). The reaction mixture was swirled by hand and kept at room temperature for 2 h. Anhydrous sodium carbonate (5 g) and molecular sieve 4A were added and stirred well for 0.5 h. The salts were removed by filtration and the solvents were evaporated *in vacuo* to yield a crystalline mass. The title compound XV was recrystallized from benzene, yield 4.23 g (90%); m.p. 90-91°, $[\alpha]_D^{24}$ -2.75° (c, 2.18 in chloroform). The n.m.r. spectrum is shown in Fig. 9 and the parameters are presented in Table VI.

Anal. Calcd. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94

Found: C, 51.76; H, 6.66%.

2. 3-O-Acetyl-5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XVI)

Compound XV (2.07 g) was dissolved in pyridine (20 ml) and acetic anhydride (20 ml) contained in a 100-ml one-necked flask. The reaction mixture was kept at room temperature for 8 h. Chloroform (30 ml) was added followed by ice-cold water. The chloroform extract was washed successively with sodium bicarbonate solution and water, dried and evaporated *in vacuo* to give the title compound XVI as a crystalline mass. Recrystallization from acetone-petroleum ether yielded 2.0 g (81.5%); m.p. 78-80°, $[\alpha]_D^{24}$ +5.25° (c, 1.88 in chloroform). The n.m.r. spectrum is shown in Fig. 10 and the parameters are shown in Table VII.

Anal. Calcd. for $C_{12}H_{18}O_7$: C, 52.55; H, 6.62
Found: C. 52.59; H, 6.60%.

3. 5,6-O-Isopropylidene-2-O-methyl-3-O-tetrahydropyranyl-D-galactonolactone (XVII)

2,2-Dimethoxypropane (50 ml) was added to compound XIV (3.87 g) dissolved in 1,2-dimethoxyethane (50 ml) containing P-toluenesulfonic acid monohydrate (0.05 g). The reaction mixture was swirled by hand and kept at room temperature for 2 h. Dihydropyran (71, 72) (50 ml) was added and the swirled solution was further kept for 0.5 h. Anhydrous sodium carbonate (5 g) and molecular sieve 4A were added and stirred well for 0.5 h. The salts were removed

by filtration and the solvents were evaporated to dryness *in vacuo* to yield a syrup. The syrup crystallized upon scratching. No attempt was made to separate the diastereoisomers (73) of the title compound XVII. The yield was 6.0 g (95%); m.p. 55-69°, $[\alpha]_D^{25}$ -24.2° (*c* 1.92 in chloroform). The n.m.r. spectrum is shown in Fig. 11.

Anal. Calcd. for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65
Found: C, 56.89; H, 7.45%.

4. 3-*O*-(1'-Ethoxyethyl)-5,6-*O*-isopropylidene-2-*O*-methyl-*D*-galactonolactone (XVIII)

2,2-Dimethoxypropane (50 ml) was added to compound XIV (3.87 g) dissolved in 1,2-dimethoxyethane (50 ml) containing *P*-toluenesulfonic acid monohydrate (0.05 g). The reaction mixture was swirled by hand and kept at room temperature for 2 h. Ethyl vinyl ether (74, 75)(50 ml) was added and the swirled solution was further kept for 1.5 h. Anhydrous sodium carbonate (5 g) and molecular sieve 4A were added and stirred well for 0.5 h. The salts were removed by filtration and the solvents were evaporated to dryness *in vacuo* to yield a syrup. T.l.c. showed the presence of only one spot. No attempt was made to separate the diastereoisomers. After further drying of the syrup under high vacuum at 50° overnight gave 6.0 g (near quantitative yield) of the title compound XVIII; $[\alpha]_D$ -21.7° (*c*, 1.98 in chloroform). The n.m.r. spectrum is shown in Fig. 12.

Anal. Calcd. for $C_{14}H_{24}O_7$: C, 55.25; H, 7.95
Found: C, 55.03; H, 7.74%.

5. 5,6-O-Isopropylidene-3-O-(2'-methoxy-2'-propyl)-2-O-methyl-D-galactonolactone (XIX)

In the preparation of compound XV, when the reaction mixture was kept longer than 2 h, the title compound XIX began to form at the expense of compound XV as revealed by t.l.c.

p-Toluenesulfonic acid monohydrate (0.005 g) was added to compound XIV (0.387 g) in 2,2-dimethoxypropane (25 ml). The reaction mixture was refluxed for 11 h and allowed to cool to room temperature. Anhydrous sodium carbonate (5 g) and molecular sieve 4A were added and stirred well for 0.5 h. The salts were removed by filtration and the solvents were evaporated to dryness in vacuo to yield a syrup (0.545 g). Rough estimation of the relative yields of compounds XIX and XV was approximately 50:50 ratio as judged from the intensity of the two spots on the thin-layer chromatogram. A benzene solution of the syrup was seeded with authentic 5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XV) and crystals of the latter were obtained, m.p. 89-91°. The title compound XIX, a syrup (crude), had $[\alpha]_D^{29}$ -37° (c, 1.43 in chloroform).

Further experiments using more 2,2-dimethoxypropane and/or prolonged heating did not seem to increase the yield of the title compound XIX as judged from the

intensity of the two spots on chromatograms, but instead led to more discoloration of the solutions (64).

VIII. Grignard reactions on derivatives of 5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XV)

1. On 3-O-acetyl-5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XVI)

Methyl magnesium iodide was prepared from magnesium (9.63 g) and methyl iodide (24.6 ml) in anhydrous ether (250 ml) under an inert atmosphere. 3-O-Acetyl-5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XVI) (6.0 g) dissolved in anhydrous ether (250 ml) was added gradually during 30 min, with stirring to the solution of methyl magnesium iodide just prepared and kept cold at 0-5°. Some white precipitate was observed during the course of addition. The reaction mixture was stirred at room temperature for 2 h. To destroy the excess methyl magnesium iodide, ether saturated with water (100 ml) was added followed by slow addition of 20% ammonium chloride solution (90 ml). The ether extract was decanted and the residue was washed with fresh portions of ether (2 x 50 ml). The combined ether extracts were evaporated *in vacuo* to give a syrup. The reaction product was purified on a column of silicic acid (100 mesh) with 45% acetone in toluene as the eluting solvent. The two fast running spots were discarded. 1-Deoxy-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-D-

galacto-heptitol (XX) was isolated as a colorless syrup (2.08 g, 36%); $[\alpha]_D^{25}$ -2.72° (c, 1.29 in 98% ethanol). There was no carbonyl absorption in the infrared spectrum. The n.m.r. spectrum is shown in Fig. 13 and the parameters are presented in Table VIII.

Anal. Calcd. for $C_{12}H_{24}O_6$: C, 54.53; H, 9.15
Found: C, 54.66; H, 8.99%.

2. On 5,6-O-isopropylidene-2-O-methyl-3-O-tetrahydropyranyl-D-galactonolactone (XVII)

Methyl magnesium iodide was prepared from magnesium (9.63 g) and methyl iodide (24.6 ml) in anhydrous ether (250 ml). The mixed diastereoisomers of 5,6-O-isopropylidene-2-O-methyl-3-O-tetrahydropyranyl-D-galactonolactone (XVII) (6.24 g) dissolved in anhydrous ether (250 ml) were added gradually, during 30 min, with stirring to the Grignard reagent just prepared and kept cold at 0-5°. The reaction mixture was stirred at room temperature for 2 h and worked up in the usual manner to yield a syrup (7.0 g). The reaction product was purified on a water-jacketed column of silicic acid (100 mesh) with 10% ethyl acetate in ether as the eluting solvent. Compound XX and the diastereoisomers of 1-deoxy-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-4-O-tetrahydropyranyl-D-galacto-heptitol (XXI) were isolated. There was no carbonyl absorption in the infrared spectrum. The n.m.r. spectrum of compound XXI is shown in Fig. 14 and the parameters are presented in Table VIII.

3. On 3-O-(1'-ethoxyethyl)-5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XVIII)

The Grignard reagent was prepared in the same manner from magnesium (9.63 g) and methyl iodide (24.6 ml) in ether (250 ml). Compound XVIII (6.0 g) dissolved in ether (250 ml) was added, again, gradually during 30 min, with stirring to the solution of methyl magnesium iodide just prepared and kept cold at 0-5°. The reaction mixture was stirred at room temperature for 2 h and worked up in the normal way to yield a syrup (6.3 + 0.7 g). T.l.c. (Silica Gel G using ether as solvent developer) showed the presence of three spots. The chromatogram is illustrated in Fig. 16. The middle bluish spot was some undesired by-product. The other two were tentatively assigned as the diastereoisomers of 1-deoxy-4-O-(1'-ethoxyethyl)-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-D-galacto-heptitol (XXII). This assignment is confirmed by the experiment X,1.

The crude reaction product was dissolved in ether and chromatographed on a water-jacketed column of silicic acid (350 g) using 10% ethyl acetate in ether as the eluting solvent. Compound XX was isolated as a syrup (2.62 g). The overlap portions (1.44 g) were rechromatographed and gave more compound XX (0.76 g). The yield of 1-deoxy-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-D-galacto-heptitol (XX) was 3.38 g (65%).

IX. β-Noviose (IV)

1. Acetylation of compound XX

Compound XX (2.0 g) was dissolved in pyridine (20 ml) and acetic anhydride (20 ml). The solution was kept at room temperature for 2 days. It was poured into ice-cold water and extracted with chloroform (2 x 20 ml). The combined chloroform extracts were washed with cold sodium bicarbonate solution and water, dried and evaporated *in vacuo* to yield a syrup (2.07). The syrup was identified by n.m.r. as 4,5-di-*O*-acetyl-1-deoxy-6,7-*O*-isopropylidene-2-*C*-methyl-3-*O*-methyl-*D*-*galacto*-heptitol (XXIII).

2. Periodic acid oxidation of compound XXIII

Compound XXIII (2.07 g, 5.32 mmole) was dissolved in glacial acetic acid (60 ml) and 0.3M periodic acid (20 ml, 6.0 mmole) was added (76). After thorough mixing, the reaction was allowed to proceed in the dark at 7° for 3.5 h. The reaction was quenched by the addition of sodium acetate (4.0 g) dissolved in water (120 ml). The aqueous solution was extracted with chloroform (5 x 20 ml). The combined chloroform extracts were washed free of iodine with 0.1 N sodium thiosulfate solution and then water, dried and evaporated *in vacuo* to yield a syrup (1.2 g). The syrup was deacetylated with triethylamine (1.4 ml) in methanol (12 ml) and water (12 ml). After being kept at room temperature for 3 h, the solvents were evaporated to dryness *in vacuo*

to yield a crystalline mass. Recrystallization from ethyl acetate-Skellysolve B afforded pure β-noviose (0.8 g); m.p. 128-130°, $[\alpha]_D^{25}$ +24° (c, 1.0 in ethanol). The melting point was undepressed in admixture with authentic β-noviose obtained from methyl α-novioside 3-(2-pyrrolecarboxylate). The n.m.r. spectrum of β-noviose is shown in Fig. 15 and the parameters are presented in Table IX.

Anal. Calcd. for $C_8H_{16}O_5$: C, 49.99; H, 8.39
Found: C, 50.20; H, 8.46%.

3. From methyl α-novioside 3-(2-pyrrolecarboxylate)

Methyl α-novioside 3-(2-pyrrolecarboxylate)* (200 mg) was dissolved in hydrazine (20 ml) and allowed to stand at room temperature for 21 h. The solvent was evaporated in vacuo and ethyl acetate was added. The undissolved material was filtered and the filtrate was evaporated under reduced pressure to give a crystalline mass. Water (10 ml) was added followed by Amberlite IR-120 (H^+) (3 ml) and heated with stirring for 19 h. The resins were filtered and the filtrate was evaporated in vacuo to yield a crystalline mass. Recrystallization from ethyl acetate-skellysolve B afforded pure material IV (90 mg); m.p. 128-130°, $[\alpha]_D^{25}$ +24° (c, 1.0 in ethanol.

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* Kindly donated by Bristol Laboratories, Syracuse, New York.

X. 2-O-Acetyl-β-noviose (XXV)

1. Removal of the acetal group of compound XXII

As mentioned previously, t.l.c. (Silica Gel G using ether or 45% acetone in toluene as solvent developers) revealed the presence of three spots in the crude reaction product of experiment VIII, 3. The chromatogram is shown in Fig. 16. The middle bluish spot was some undesired by-product. The other two were believed to be the diastereoisomers of 1-deoxy-4-O-(1'-ethoxyethyl)-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-D-galacto-heptitol (XXII). The crude compound XXII (1.0 g) was dissolved in aqueous acetic acid (10 ml). It was kept at room temperature for 2 h and freeze-dried in high vacuo. Thin-layer chromatography showed the presence of only two spots. The slow-moving spot had the same Rf value as authentic compound XX. It was purified by chromatography and the n.m.r. spectrum was identical to that of 1-deoxy-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-D-galacto-heptitol (XX).

2. Acetylation of compound XXII

Compound XXII (10.0 g; the crude reaction product of experiment VIII, 3) was dissolved in pyridine (80 ml) and acetic anhydride (80 ml). The resulting solution was kept at room temperature for 19 h. It was poured into ice-cold water and extracted with chloroform (250, 2 x 100 ml).

The combined chloroform extracts were washed with cold sodium bicarbonate solution and water, dried and evaporated *in vacuo* to yield a syrup (10.8 g); $[\alpha]_D^{30}$ -27.4° (*C*, 1.54 in chloroform). Thin-layer chromatography showed the presence of three spots. The chromatogram is illustrated in Fig. 16. The bluish spot was some undesired by-product. The other two were the diastereoisomers of 5-*O*-acetyl-1-deoxy-4-*O*-(1'-ethoxyethyl)-6,7-*O*-isopropylidene-2-*C*-methyl-3-*O*-methyl-*D*-*galacto*-heptitol (XXIV).

3. Periodic acid oxidation of compound XXIV

Compound XXIV (10.0 g, 26.4 mmole; the crude reaction product of experiment X, 2) was dissolved in glacial acetic acid (300 ml) and 0.3M periodic acid (100 ml, 30 mmole) was added. After thorough mixing, the reaction was allowed to proceed in the dark at 7° for 3.5 h. The solution was immediately passed through IRA-400 ($\bar{O}AC$) (80 g) (77) ion exhange resin contained in a water-jacketed column. The column was washed free of the sugar with distilled water. The solvents were evaporated *in vacuo* to give a semi-crystalline syrup (6.0 g). Ether was added and yellowish crystals were obtained. The crystals were filtered by suction and washed a few times with fresh portions of ether. Recrystallization from ethyl acetate-Skellysolve B afforded pure 2-*O*-acetyl-β-noviose (XXV) (2.62 g); m.p. 142-145°, $[\alpha]_D^{25}$ +60° (*c*, 1.76 in 98% ethanol). The rotation decreased to +26° after the solution

was kept at room temperature for 50 h. The overall yield of 2-O-acetyl-β-noviose (XXV) from 3-O-(1'-ethoxyethyl)-5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XVIII) was about 43%. The n.m.r. spectrum of compound XXV is shown in Fig. 17 and the parameters are presented in Table IX. The infrared spectrum is shown in Fig. 18.

Anal. Calcd. for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75
Found: C, 51.50; H, 7.72%

4. Deacetylation of compound XXV

Compound XXV (200 mg) was dissolved in methanol (2 ml) and water (2 ml). Triethylamine (0.24 ml) was added. The solution was kept at room temperature for 3 h. Solvents were evaporated to dryness in vacuo to yield a crystalline mass (150 mg). Recrystallization from ethyl acetate-Skellysolve B afforded pure β-noviose (IV); m.p. 128-130°, $[\alpha]_D^{25}$ +24° (c, 1.0 in ethanol). The melting point was undepressed in admixture with authentic β-noviose (IV).

5. β-Noviose from compound XXIV

Compound XXIV (1.0 g, 2.64 mmole; the crude reaction product of experiment X, 2) was dissolved in glacial acetic acid (30 ml) and aqueous 0.3M periodic acid (10 ml, 3 mmole). After thorough mixing, the reaction was allowed to proceed in the dark at 7° for 3.5 h. Acetic anhydride (100 ml)

was added and the solution turned opalescent immediately. The reaction was followed by thin-layer chromatography. After it was kept at room temperature for 19 h, the solution became clear. Chloroform (2 x 25 ml) was added and the combined chloroform extracts were washed with water, sodium bicarbonate solution, 0.1N sodium thiosulfate solution and then water. The chloroform layer was dried and evaported *in vacuo* to give a syrup. Methanol (2 ml) and water (2 ml) were added followed by triethylamine (0.24 ml). The reaction mixture was kept at room temperature for 3 h with occasional swirling. The solvents were evaporated under reduced pressure to yield a crystalline mass. Recrystallization from ethyl acetate-Skellysolve B afforded pure β-noviose (0.18 g); m.p. 128-130°. The melting point was undepressed in admixture with authentic β-noviose.

XI Derivatives of noviose

1. β-Noviose triacetate (XXVI)

a. From 2-*O*-acetyl-β-noviose (XXV)

Compound XXV (10.0 g) was dissolved in acetic anhydride (50 ml) and pyridine (50 ml) kept at -15°. The reaction was allowed to continue at -15° for 4 h. The solution was poured into ice-water and extracted with chloroform (2 x 250 ml). The combined chloroform extracts were washed with sodium bicarbonate solution and water, dried and evaporated *in vacuo* to give a syrup (13.5 g, near

quantitative yield).

Syrupy β-noviose triacetate (200 mg) was purified by chromatography on silicic acid using 30% ethyl acetate in chloroform as eluent. Pure compound XXVI had $[\alpha]_D^{23}$ +50° (c, 1.26 in chloroform). The n.m.r. spectrum of this compound is shown in Fig. 19 and the parameters are presented in Table X.

Anal. Calcd for $C_{14}H_{22}O_8$: C, 52.82; H, 6.97 Found: C, 52.80; H, 6.96%.

b. From β-noviose (IV)

β-Noviose (100 mg) was dissolved in acetic anhydride (2 ml) and pyridine (2 ml) kept at -15°. The reaction was allowed to continue at -15° for 4 h, and worked up in the usual manner to yield a syrup. The syrup was purified by chromatography on silicic acid using 30% ethyl acetate in chloroform as eluent. Pure compound XXVI (135 mg) was obtained. The n.m.r. spectrum of the product is identical to that of the β-noviose triacetate obtained from compound XXV.

2. α-Noviose triacetate (XXVIα)

Compound XXV (100 mg) was dissolved in acetic anhydride (2 ml) and anhydrous zinc chloride (20 mg) was added. The reaction mixture was kept at 50° for 2 h and worked up in the usual manner to yield a syrup (130 mg). Purification on a column of silicic acid gave a syrup which consisted of α-noviose triacetate and a small amount of the β-anomer

(XXVI) as indicated by the n.m.r. spectrum, which is shown in Fig. 20. The n.m.r. parameters are presented in Table X. The purified syrup had $[\alpha]_D^{23}$ -8.0 (c, 2.11 in chloroform).

3. Mixture of 2,3-di-O-acetylnoviosyl chlorides (XXVII)

Compound XXVI (3.0 g, 9.42 mmole) was dissolved in pure, dry chloroform (15 ml), powdered aluminum chloride (0.67 g, 5.0 mmole)was added, and the mixture was shaken at room temperature for 30 min (78). Aluminum chloride gradually disappeared and was replaced by a fine white precipitate. Dry benzene (30 ml) was added, followed by dry silicic acid (1.0 g). The precipitate was removed by filtration and washed with additional dry benzene (5 ml). The filtrate was evaporated at room temperature under reduced pressure to yield a syrup (2.77 g), from which last traces of solvents were removed in a high vacuum. The syrupy title compound XXVII had $[\alpha]_D^{25}$ -47° (c, 2.15 in benzene). Thin-layer chromatogram revealed the presence of three spots. The n.m.r. spectrum is reproduced in Fig. 21 and shows the product to be a mixture. The compounds were too labile to allow chromatographic separation. Characterization as the glycosyl chlorides was provided by the following experiment in which the material was converted to the orthoester (XXVIII).

4. 3-O-Acetyl-β-noviose 1,2-(methyl orthoacetate) (XXVIII)

2,3-Di-O-acetylnoviosyl chlorides (XXVII) (3.0 g, 10.2 mmole) and tetraethylammonium chloride (79, 80) (1.70 g, 10.2 mmole) were dissolved in pure, dry chloroform (15 ml). Anhydrous methanol (3 ml) and 2,6-lutidine (3 ml) were added and the reaction mixture was kept at room temperature for 2 h. Chloroform (50 ml) was added and washed with cold water (7 x 200 ml), sodium bicarbonate solution and then cold water, dried and evaporated under reduced pressure to yield a syrup. Last traces of solvents were removed in a high vacuum at 40° to give the title compound (2.2 g, 74%). Only the exo isomer of compound XXVIII was obtained as indicated by the n.m.r. spectrum, which is shown in Fig. 22. The n.m.r. parameters are presented in Table XI. The syrup (200 mg) was purified on a column of silicic acid with 0.3% 2,6-lutidine and 50% ethyl acetate in toluene as the eluting solvent. The pure material XXVIII had $[\alpha]_D^{23}$ +74° (c, 1.09 in chloroform).

Anal. Calcd. for $C_{13}H_{22}O_7$: C, 53.78; H, 7.64
Found: C, 53.55; H, 7.60%.

5. β-Noviose 1,2-(methyl orthoacetate) (XXIX)

Compound XXVIII (200 mg) was dissolved in absolute methanol (10 ml). Barium methoxide in methanol, (0.5 N, 5 ml) was added with cooling. After 10 min, carbon dioxide was bubbled into the solution. The precipitated barium carbonate was removed by filtration and washed

with additional methanol (2 ml). The filtrate was evaporated *in vacuo* to give a syrup and ether (25 ml) was added. The undissolved material was filtered off and discarded. Evaporation of the solvent under reduced pressure afforded a syrup which crystallized on standing (130 mg, 76%). The title compound XXIX had m.p. 62-65°, $[\alpha]_D^{27}$ +25° (*c*, 1.01 in chloroform). The n.m.r. spectrum is shown in Fig. 23 and the parameters are presented in Table XI.

Anal. Calcd. for $C_{11}H_{20}O_6$: C, 53.21; H, 8.12
Found: C, 53.31; H, 8.09%.

In an early attempt to purify β-noviose 1,2-(methyl orthoacetate) (XXIX) by chromatography on a column of silicic acid with 0.3% 2,6-lutidine and 45% acetone in toluene as the eluting solvent, the material isolated was 2-*O*-acetyl-β-noviose (XXV).

XII. Condensation of 3,4,6-tri-*O*-acetyl-β-*D*-mannopyranose 1,2-(methyl orthoacetate) (XXX) with phenol

1. Preparation of 3,4,6-tri-*O*-acetyl-β-*D*-mannopyranose 1,2-(methyl orthoacetate)(XXX).

The *exo* isomer of compound XXX was prepared according to the published procedure (81) and had m.p. 111-113°, $[\alpha]_D^{25}$ -24° (*c*, 1.0 in chloroform).

2. Condensation with antimony pentachloride as catalyst

The volume of methylene chloride containing the required antimony pentachloride was small in all cases.

a. Using 0.05 mole of acid per mole of orthoester

Compound XXX (2.0 g, 5.52 mmole) and phenol (1.04 g, 11.04 mmole) were dissolved in methylene chloride (20 ml). Antimony pentachloride (0.0353 ml, 0.276 mmole) in methylene chloride was added and the solution was kept at room temperature for 0.5 h. Chloroform (50 ml) was added, and the solution was washed with cold N sodium hydroxide solution (5 x 200 ml) and water (2 x 200 ml), dried and evaporated under reduced pressure to yield a syrup (1.41 g). Thin-layer chromatography showed the product to consist of at least five spots. The chromatogram is illustrated in Fig. 24. The reaction mixture (0.5 g) was separated on a dry column of Silica Gel G using 50% ethyl acetate in toluene as the eluting solvent. The four major compounds were identified by n.m.r. as phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI),methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII), phenyl 3,4,6-tri-O-acetyl-α-D-mannopyranoside, and methyl 3,4,6-tri-O-acetyl-α-D-mannopyranoside, respectively. The latter two compounds gave XXXI and XXXII, respectively, on acetylation with acetic anhydride in the presence of pyridine.

Phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI) was obtained as a syrup, which was induced to crystallize from 98% ethanol by seeding; m.p. 79-80°, $[\alpha]_D^{25}$ +70.5° (c, 1.40 in chloroform). [Literature (82), m.p. 79-80°, $[\alpha]_D$ +74.9° (chloroform)]. Compound XXXI was synthesized by the Helferich method (83) and isolated as a crystalline material, m.p. 79-80°. The n.m.r. spectrum of the prepared phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI) was identical to that of compound XXXI obtained from the condensation of 3,4,6-tri-O-acetyl-β-D-mannopyranose 1,2-(methyl orthoacetate) (XXX) with phenol. The n.m.r. spectrum of phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI) is shown in Fig. 25.

Methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII) was obtained as a crystalline mass. Recrystallization from 95% ethanolafforded pure material; m.p. 63-64°, $[\alpha]_D^{26}$+45° (c, 1.36 in chloroform). The melting point was undepressed in admixture with authentic methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII). Compound XXXII was reported in the literature (84) to have m.p. 65°, $[\alpha]_D$ +49.1° (chloroform). The n.m.r. spectrum of this compound is shown in Fig. 26.

The crude product (0.65 g) from the condensation of 3,4,6-tri-O-acetyl-β-D-mannopyranose 1,2-(methyl orthoacetate) (XXX) with phenol was acetylated with acetic anhydride (10 ml) in the presence of pyridine (10 ml).

The solution was kept at room temperature for 5 h. Chloroform (25 ml) was added, and the solution was washed with cold sodium bicarbonate solution and water, dried and evaporated *in vacuo* to give a syrup (0.58 g). The syrup consisted of phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI) (~55%) and methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII) (~45%), as indicated by the n.m.r. spectrum. This ratio was found by comparison of the integration values for the signals of the phenyl ring protons at τ2.56-3.17 in compound XXXI and the methoxyl protons at τ6.63 in compound XXXII. A thin-layer chromatogram indicated the presence of two major components.

b. Using 1.0 mole of acid per mole of orthoester

Compound XXX (500 mg, 1.38 mmole) and phenol (260 mg, 2.76 mmole) were dissolved in methylene chloride (7 ml). Antimony pentachloride (0.176 ml, 1.38 mmole) in methylene chloride was added. The resulting brown solution was kept at room temperature for 0.5 h, and worked up in the usual manner to yield a syrup (263 mg). The crude product (197 mg) was acetylated with acetic anhydride in the presence of pyridine, and worked up in the normal way to give a syrup (155 mg). The n.m.r. spectrum indicated the presence of phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI) (~59%) and methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII) (~41%).

c. Using 20 moles of phenol per mole of orthoester

Compound XXX (500 mg. 1.38 mmole) and phenol (2.260 g, 27.6 mmole) were dissolved in methylene chloride (10 ml). Antimony pentachloride (0.009 ml, 0.069 mmole) in methylene chloride was added, and the solution was kept at room temperature for 0.5 h. Chloroform (50 ml) was added, and the solution was washed with cold N sodium hydroxide solution (2 l), water (500 ml), dried and evaporated in vacuo to yield a syrup (450 mg). The crude product (157 mg) was dissolved in acetic anhydride (5 ml) and pyridine (5 ml). The solution was kept at room temperature for 5 h and worked up in the usual manner to give a syrup. The n.m.r. spectrum, which is shown in Fig. 27, indicated the presence of phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI) (~87%) and methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII) (~13%).

3. Fusion at elevated temperature

Compound XXX (500 mg, 1.38 mmole) and phenol (260 mg, 2.76 mmole) were vigorously stirred in an oil bath at 160° for 1 h. The melt, after cooling, was dissolved in chloroform (25 ml), and washed with cold N sodium hydroxide solution (4 x 100 ml), water (2 x 100 ml), dried and evaporated in vacuo to yield a syrup (432 mg). The n.m.r. spectrum of the product indicated the presence of 32% of the unreacted starting material, 47% of phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI), and 21% of methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII).

These yields were estimated by comparison of the integration values for the signals of the methoxyl protons at τ6.73 or the C-methyl protons at τ8.27 in compound XXX, the phenyl ring protons at τ2.68-3.0 in compound XXXI, and the methoxyl protons at τ6.63 in compound XXXII.

4. Condensations with mercuric bromide as catalyst

A volume of 2 ml of 1,2-dichloroethane contained about 50 mg of mercuric bromide.

Compound XXX (500 mg, 1.38 mmole) and phenol (260 mg, 2.76 mmole) were dissolved in nitromethane (7 ml). Mercuric bromide (24.8 mg, 0.069 mmole) in 1,2-dichloroethane was added (85). The solution was refluxed for 1.5 h. Chloroform (25 ml) was added to the cooled reaction mixture, and the solution was washed with cold N sodium hydroxide solution (4 x 100 ml), water (2 x 100 ml), dried and evaporated *in vacuo* to yield a syrup (420 mg). Thin-layer chromatography of the product showed only two spots. The product (209 mg) was dissolved in acetic anhydride (5 ml) and pyridine (5 ml). The solution was kept at room temperature for 5 h, and worked up in the usual manner to give a syrup (200 mg). Again, only two spots, which had the same Rf values as found before acetylation, were revealed by t.l.c. The n.m.r. spectrum of the acetylated product was unchanged from the one taken before acetic anhydride and pyridine had been added.

The syrup consisted of phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI) (~15%) and methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII) (~85), as indicated by the n.m.r. spectrum which is shown in Fig. 28.

In another experiment, nitromethane (14 ml) containing compound XXX (1.0 g, 2.76 mmole), phenol (520 mg, 5.52 mmole) and mercuric bromide (49.6 mg, 0.138 mmole) in 1,2-dichloroethane, were distilled for 1.5 h at atmospheric pressure with addition of fresh nitromethane to keep the volume constant. The cooled reaction mixture was worked up in the usual manner to yield a syrup (888 mg). The syrup consisted of phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI) (~20%) and methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII) (~80%), as indicated by the n.m.r. spectrum.

In another experiment, nitromethane (40 ml) containing compound XXX (1.0 g, 2.76 mmole) and phenol (520 mg, 5.52 mmole) were distilled at atmospheric pressure. Two fractions containing 13 and 19 ml of distillates were collected. Traces of methanol were detected in the first fraction by n.m.r. spectroscopy, although none could be detected in the second fraction. A small portion (2.37 g) of the residue in the flask was evaporated *in vacuo* to give a syrup. The n.m.r. spectrum indicated the presence of about 60% of compound XXX. Mercuric bromide (49.6 mg, 0.138 mmole) in 1,2-dichloroethane was added to the

remaining solution (12.64 g) and refluxed for 1.5 h. The cooled reaction mixture was worked up in the normal way to give a syrup (695 mg). The syrup consisted of phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI) (~33%) and methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII) (~67%), as indicated by the n.m.r. spectrum.

5. With P-toluenesulfonic acid as catalyst

Compound XXX (500 mg, 1.38 mmole) and phenol (260 mg, 2.76 mmole) were dissolved in methylene chloride (7 ml). Dry P-toluenesulfonic acid in methylene chloride (3.82 ml, 0.69 mmole by titration) was added. The reaction was followed by n.m.r. spectroscopy by observing the disappearance of the signals for the methoxyl protons at τ6.73 and the C-methyl protons at τ8.27. After 24 h at room temperature, chloroform (25 ml) was added, The solution was washed with cold N sodium hydroxide solution (4 x 100 ml) and water (2 x 100 ml), dried and evaporated in vacuo to yield a syrup (342 mg). The product (323 mg) was acetylated with acetic anhydride in the presence of pyridine, and worked up in the usual manner to give a syrup (251 mg). The n.m.r. spectrum of the product indicated the presence of phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI) (~69%), methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII) (~13%), and a tosyl derivative (~18%) which had signals centered at τ2.2, 2.65, 7.55. Thin-layer chromatography of the product revealed

the presence of at least four spots of which the two fastest spots were compounds XXXI and XXXII, respectively.

XIII Condensation of 3-O-acetyl-β-noviose 1,2-(methyl orthoacetate)(XXVIII) with phenol.

1. With antimony pentachloride as catalyst

Compound XXVIII (500 mg, 1.72 mmole) and phenol (324 mg, 3.44 mmole) were dissolved in methylene chloride (10 ml). Antimony pentachloride (0.01 ml, 0.086 mmole) in methylene chloride was added, and the solution was kept at room temperature for 0.5 h. The reaction mixture was worked up in the usual manner to yield a syrup (448 mg). The product was dissolved in acetic anhydride and pyridine, and the solution was kept at room temperature for 5 h. The resulting solution was worked up in the normal way to give a syrup. Thin-layer chromatography of the product showed three spots. The chromatogram is illustrated in Fig. 29. The mixture was separated on a dry column of Silica Gel G using 20% ethyl acetate in toluene as the eluting solvent. The three compounds were identified by n.m.r. as phenyl 2,3-di-O-acetyl-α-novioside (XXXIII), methyl 2,3-di-O-acetyl-α-novioside (XXXIV), and methyl 2,3-di-O-acetyl-β-novioside (XXXV), respectively. By comparison of the integration values for the signals of the phenyl ring protons at τ2.78-3.25 in compound XXXIII, and the 1-methoxyl protons at τ6.65 in compounds XXXIV and XXXV, the product contained about 15% of phenyl

2,3-di-O-acetyl-α-novioside (XXXIII). Judging from the intensity of the spots on the thin-layer chromatogram, methyl 2,3-di-O-acetyl-α-novioside (XXXIV) was formed in a larger proportion than methyl 2,3-di-O-acetyl-β-novioside (XXXV).

Phenyl 2,3-di-O-acetyl-α-novioside (XXXIII) had $[\alpha]_D^{26}$ -42.5° (c, 2.37 in chloroform). The n.m.r. spectrum of this compound is shown in Fig. 30. The syrupy methyl 2,3-di-O-acetyl-α-novioside (XXXIV) had $[\alpha]_D^{26}$ -18° (c, 1.59 in chloroform). [Literature (19), m.p. 62-64°, $[\alpha]_D^{24}$ -20.4° (c, 0.973 in 95% ethanol)]. The n.m.r. spectrum of compound XXXIV is shown in Fig. 31. Methyl 2,3-di-O-acetyl-β-novioside (XXXV) had $[\alpha]_D^{26}$ +48° (c, 0.8 in chloroform), and its n.m.r. spectrum is shown in Fig. 32. The parameters of compounds XXXIII, XXXIV, and XXXV are presented in Table XIII.

Deacetylation of compounds XXXIV and XXXV with barium methoxide in absolute methanol gave the α- and β-methyl noviosides, respectively. The n.m.r. spectra of the latter two compounds are shown in Fig. 33 and 34, and the parameters are presented in Table XIV.

2. With mercuric bromide as catalyst

a. Using 2.0 moles of phenol per mole of orthoester

Compound XXVIII (500 mg, 1.72 mmole) and phenol (324 mg, 3.44 mmole) were dissolved in nitromethane (7 ml). Mercuric bromide (31.4 mg, 0.086 mmole) in 1,2-dichloroethane

was added. The solution was refluxed for 1.5 h, and chloroform (50 ml) was added to the cooled reaction mixture. The solution was worked up in the usual manner to yield a syrup (450 mg). Thin-layer chromatography of the product revealed three spots. The mixture was separated on a dry column of Silica Gel G using 20% ethyl acetate in toluene as the eluting solvent. The compounds were identified by n.m.r. as XXXIII, XXXIV, and XXXV, respectively. The yield of phenyl 2,3-di-O-acetyl-α-novioside (XXXIII) was about 18% as indicated by the n.m.r. spectrum. Again, methyl 2,2-di-O-acetyl-α-novioside (XXXIV) was formed in a larger proportion than methyl 2,3-di-O-acetyl-β-novioside (XXXV) as judged from the intensity of the spots on the thin-layer chromatogram.

b. Using 20 moles of phenol per mole of orthoester

Compound XXVIII (250 mg, 0.86 mmole) and phenol (1.62 g, 17.2 mmole) were dissolved in nitromethane (5 ml). Mercuric bromide (15.7 mg, 0.043 mmole) in 1,2-dichloroethane was added, and the solution was refluxed for 1.5 h. Chloroform (25 ml) was added to the cooled reaction mixture, and the solution was washed with cold N sodium hydroxide solution (1 l), water (250 ml), dried and evaporated in vacuo to give a syrup (208 mg). The yield of phenyl 2,3-di-O-acetyl-α-novioside (XXXIII) was about 36% as indicated by the n.m.r. spectrum. Compound XXXIV was formed in a larger proportion than XXXV as judged from the thin-layer chromatogram.

XIV. Condensation of 3-O-acetyl-β-noviose 1,2-(methyl orthoacetate) (XXVIII) with β-naphthol using mercuric bromide as catalyst

1. Using 2.0 moles of β-naphthol per mole of orthoester

Compound XXVIII (250 mg, 0.86 mmole) and β-naphthol (248 mg, 1.72 mmole) were dissolved in nitromethane (5 ml). Mercuric bromide (15.7 mg, 0.043 mmole) in 1,2-dichloroethane was added, and the solution was refluxed for 1.5 h. Chloroform (25 ml) was added to the cooled reaction mixture, and the solution was washed with cold N sodium hydroxide solution (4 x 100 ml), water (2 x 100 ml), dried and evaporated *in vacuo* to yield a syrup (210 mg). Thin-layer chromatography showed the product to consist of at least four components. The chromatogram is illustrated in Fig. 35. The mixture was separated on a dry column of Silica Gel G using 5% ethyl acetate in chloroform as the eluting solvent.

The first eluted compound was identified by n.m.r. to be β-naphthyl 2,3-di-O-acetyl-α-novioside (XXXVI), $[\alpha]_D^{26}$ -65.5° (*c*, 1.83 in chloroform). The n.m.r. spectrum of this compound is shown in Fig. 36 and the parameters are presented in Table XIII. The third and fourth eluted compounds were shown by n.m.r. to be virtually identical with methyl 2,3-di-O-acetyl-α-novioside (XXXIV) and methyl 2,3-di-O-acetyl-β-novioside (XXXV), respectively.

The second eluted material could not be identified. Judging from the intensity of the spots on the thin-layer chromatogram, compound XXXIV was formed in a larger proportion than compound XXXV. By comparison of the integration values for the signals of the β-naphthyl ring protons at τ2.30-2.92 in compound XXXVI and the 1-methoxyl protons at τ6.65 in compounds XXIV and XXXV, the yield of β-naphthyl 2,3-di-O-acetyl-α-novioside (XXXVI) was estimated to be less than 17%.

2. Using 20 moles of β-naphthol per mole of orthoester

Compound XXVIII (250 mg, 0.86 mmole) and β-naphthol (2.48 g, 17.2 mmole) were dissolved in nitromethane (7 ml). Mercuric bromide (15.7 mg, 0.043 mmole) in 1,2-dichloroethane was added, and the solution was refluxed for 1.5 h. The reaction mixture was worked up in the usual manner to yield a syrup (250 mg). Thin-layer chromatography revealed the product to consist of at least four components. The yield of β-naphthyl 2,3-di-O-acetyl-α-novioside (XXXVI) was estimated to be less than 45% as indicated by the n.m.r. spectrum. Again, compound XXXIV was formed in a larger proportion than compound XXXV as judged from the intensity of the spots on the chromatogram.

DISCUSSION

The main purpose of this research was to devise a facile synthesis of β-noviose (IV). A second objective was to determine whether 3-O-acyl-β-noviose 1,2-(methyl orthoacetate) could be a useful intermediate for the preparation of aryl 3-O-acyl-α-noviosides with structures related to the antibiotics novobiocin (I) and coumermycin A_1 (II). Vaterlaus and co-workers (24, 25) have published the results of an extensive investigation of the Koenigs-Knorr reaction (139) involving 2,3-O-carbonylnoviosyl halides. The interest in the synthesis of noviosides from 1,2-orthoesters of noviose arose from the recent publication by Kochetkov and co-workers (141) who described the stereospecific formation of 1,2-trans glycosides from 1,2-O-alkyl orthoesters in good yields.

The synthetic route to 2-O-acetyl-β-noviose (XXV), which was finally established in this research and which proceeded in 35% overall yield from 1,6-anhydro-3,4-O-isopropylidene-β-D-galactose (XI), is outlined in Fig. 37. This starting material is readily available (86) from either D-galactose or α-lactose monohydrate.

Micheel (87) synthesized 1,6-anhydro-β-D-galactopyranose (β-galactosan) from tetra-O-acetyl-β-D-galactopyranosyl trimethylammonium bromide, obtained by treating tetra-O-acetyl-α-D-galactopyranosyl bromide with

Fig. 37. Synthetic route of 2-O-acetyl-β-noviose (XXV).

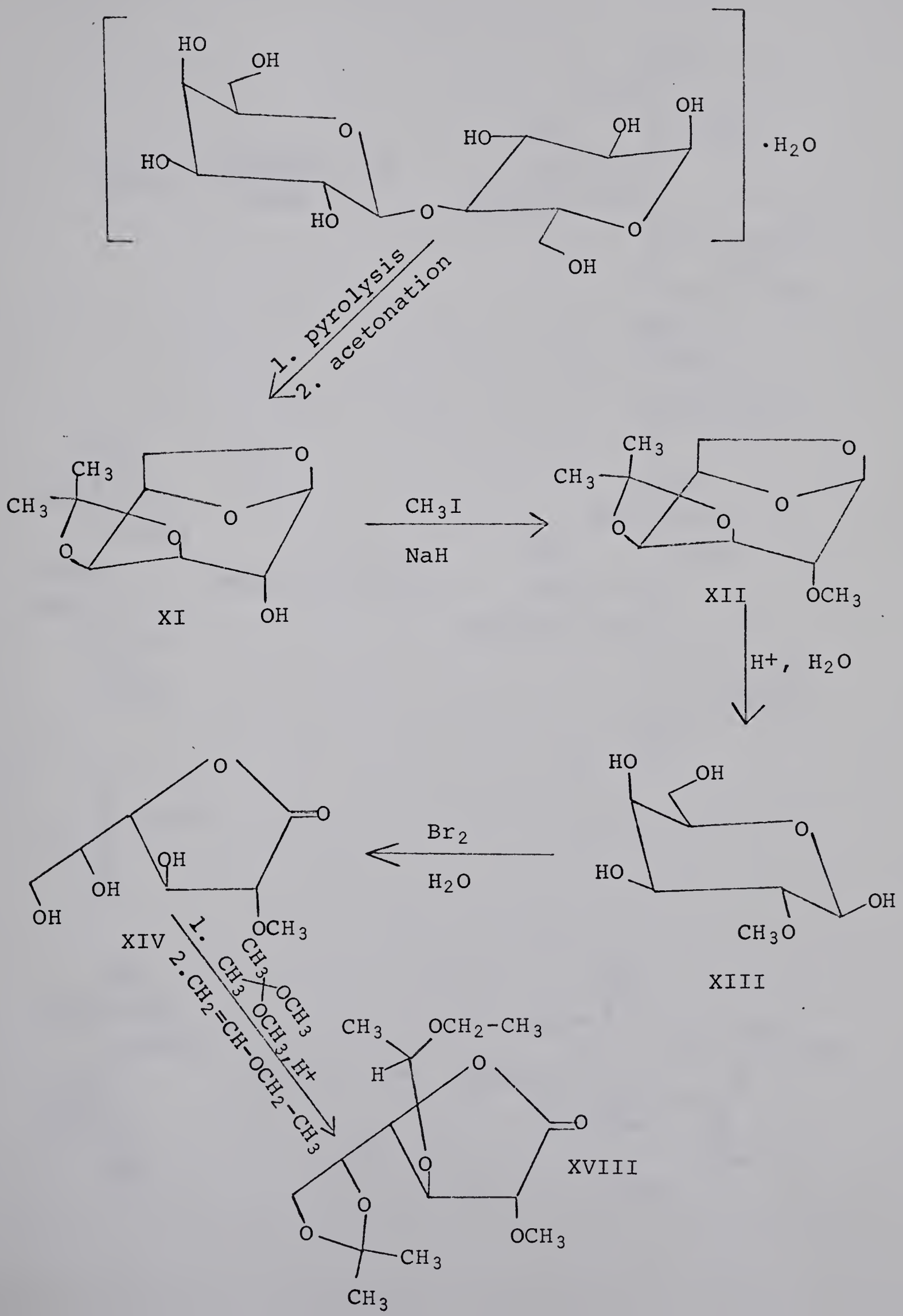
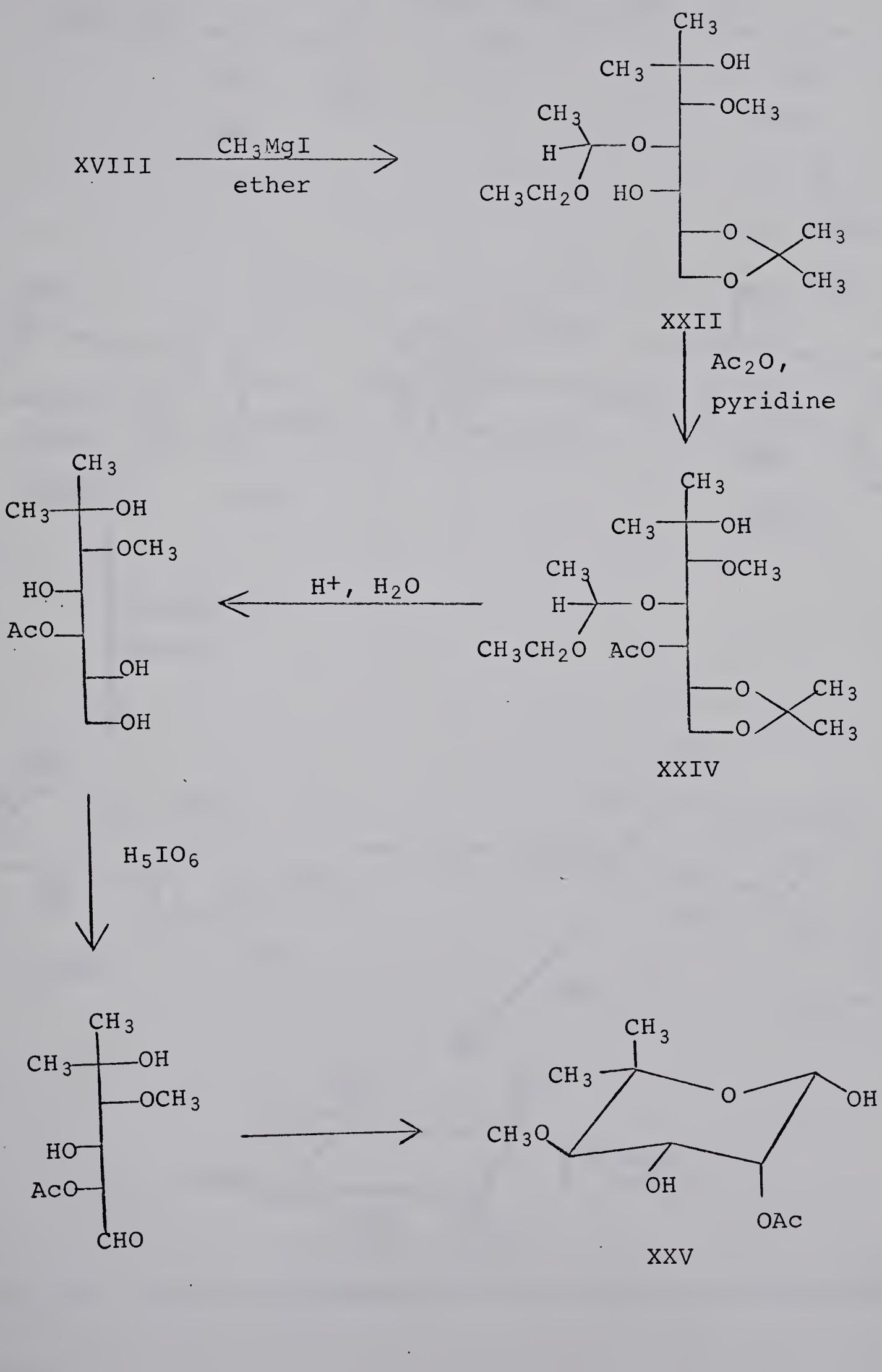


Fig. 37 (cont'd)



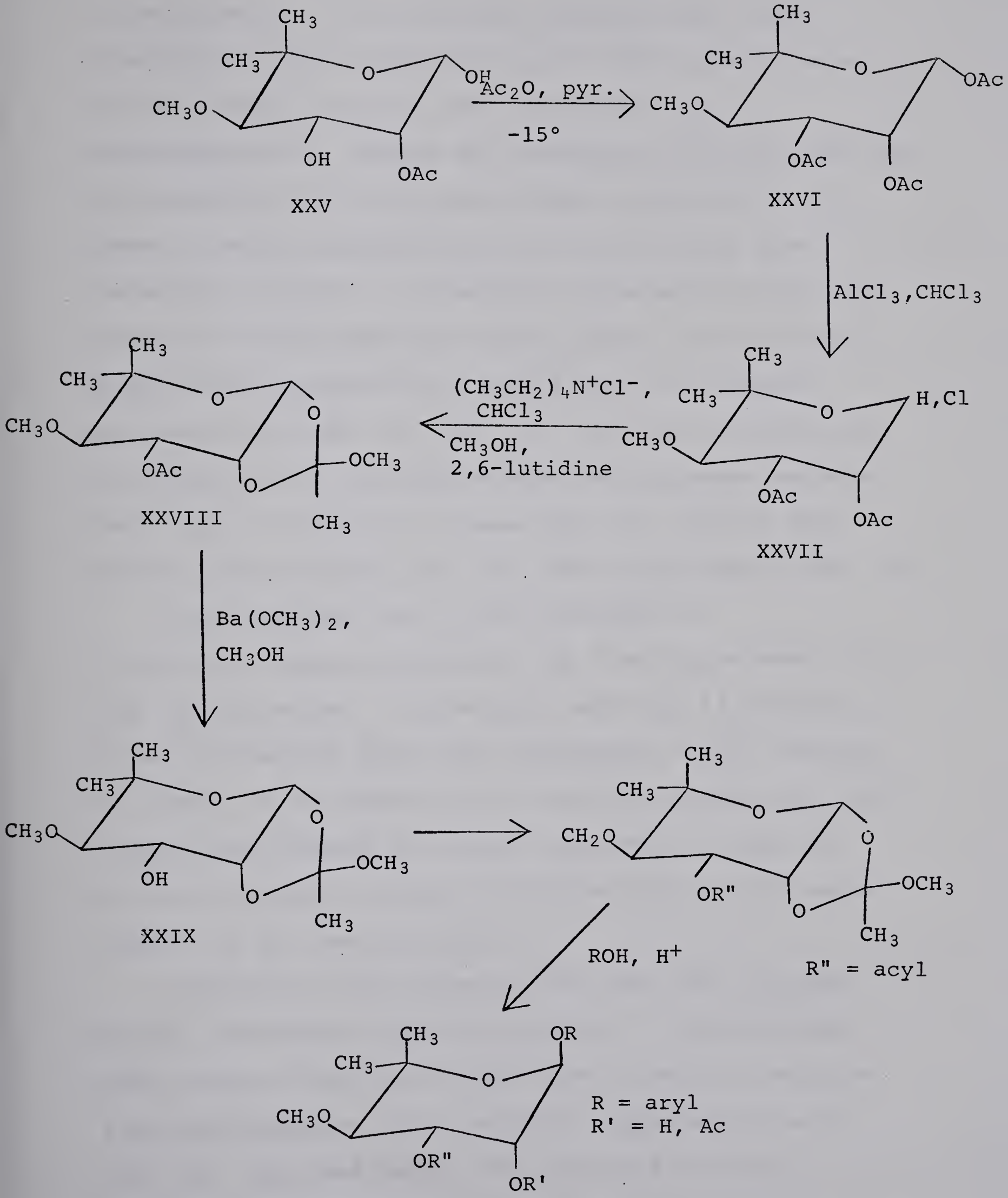


Fig. 38. Route of synthesis of aryl 3-O-acyl-α-noviosides.

trimethylamine. This quaternary ammonium salt, when treated with barium hydroxide, splits off trimethylamine and the acetyl groups to form 1,6-anhydro-β-D-galactopyranose. Micheel and co-workers (88) also described the preparation of this anhydro sugar by the action of bases or anion exchange resins (in the OH form) upon galactosyl fluoride. 1,6-Anhydro-β-D-galactopyranose was obtained in good yield by treating phenyl tetra-O-acetyl-D-galactopyranosides with a strong base, for example, potassium hydroxide (58, 89). The reaction mechanism for the formation of 1,6-anhydro-β-D-galactopyranose has been dealt with in detail by Coleman (94, 95), Lemieux (96), Ballou (97) and others (98, 99), and is outlined in Fig. 39.

It is believed that in the formation of 1,6-anhydro-β-D-galactopyranose (3) from the β-isomers (1), the corresponding 1,2-anhydro sugar (2) is produced as an intermediate which then rearranges, in the presence of a base, to the product (3). For the α-isomers (4), the reaction may proceed by a slow, nucleophilic attack on C-1 by the primary hydroxyl of C-6, with the simultaneous removal of the leaving group X.

Pyrolysis of the polysaccharide agar (90) *in vacuo* yields 1,6-anhydro-β-D-galactopyranose. α-D-Galactose, under similar conditions, gives rise to both 1,6-anhydro-β-D-galactopyranose and 1,6-anhydro-α-D-galactofuranose (91, 92). Hann and Hudson (60) pyrolyzed α-lactose monohydrate under reduced pressure and obtained the

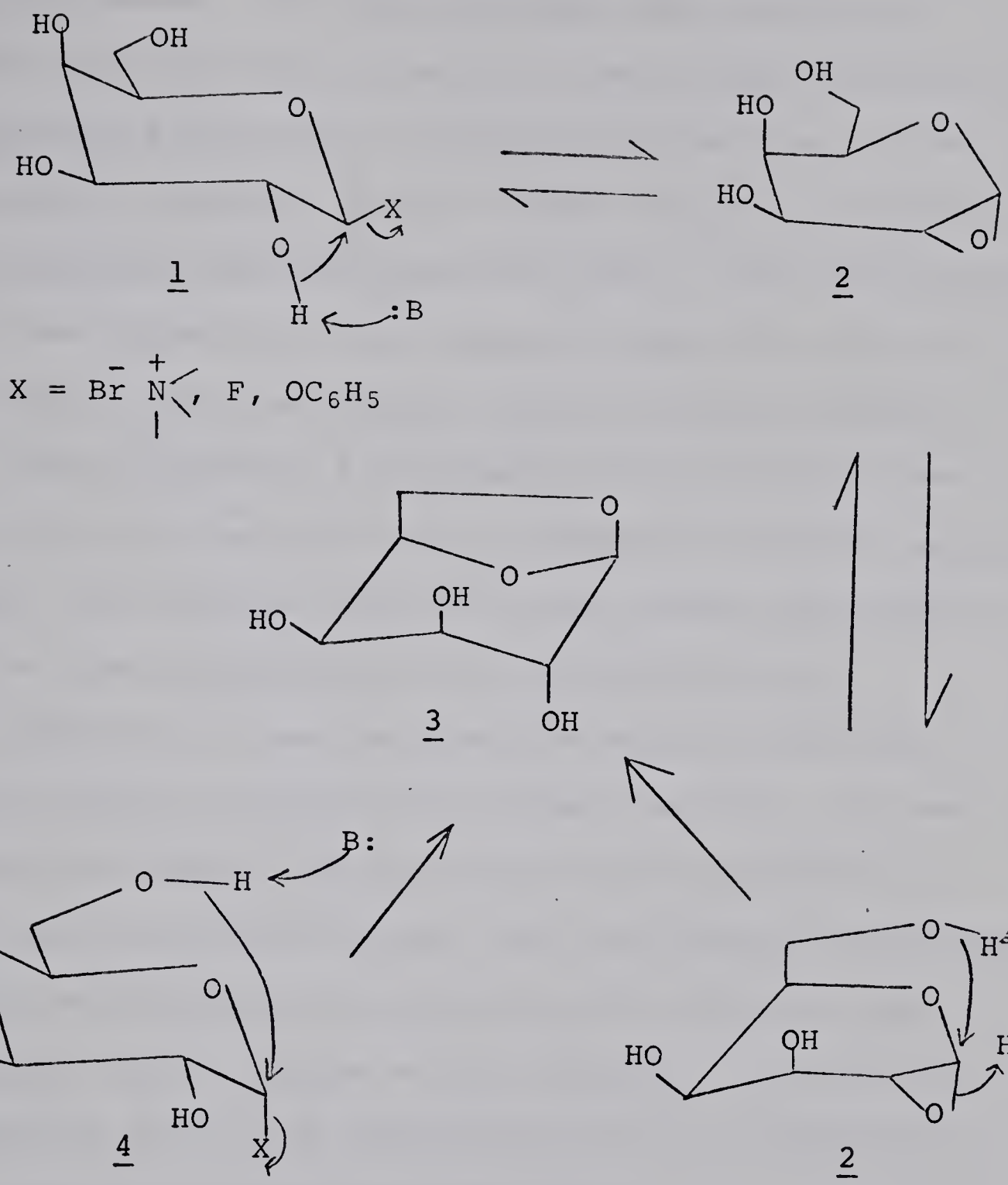


Fig. 39. Preparation of 1,6-anhydro-β-D-galactopyranose.

1,6-anhydrides of both β-D-glucopyranose and β-D-galactopyranose. The two anhydrides were separated through the fact that, because of the 3,4-cis-configuration, the galactose derivative condensed with acetone in the presence of anhydrous copper sulfate to give 1,6-anhydro-3,4-O-isopropylidene-β-D-galactose (XI). This attractive route was followed in this research under the conditions specified by Hann and Hudson (60) but without success. Only trace amounts of 1,6-anhydro-3,4-O-isopropylidene-β-D-galactose (XI) was isolated. Attempts to obtain compound XI from the reaction mixture by high vacuum distillation were no more successful than by crystallization.

Therefore, it was necessary to modify either the heating stage or the work up process, or both. In one of the experiments, the pyrolyzates were purified on a large charcoal-Celite column, and the fractions containing the two anhydrides were acetonated with acetone using anhydrous copper sulfate as the catalyst. In this way, compound XI was indeed obtained but not in satisfactory yield and the procedure was laborious.

In the procedure finally adopted, special attention was made to ensure uniform and rapid heating of the 1-liter flask containing the α-lactose monohydrate by the manipulation of two Bunsen burners with large luminous flames. The apparatus is shown in Fig. 5. Copper powder was mixed with both the second and third charge to

improve heat transfer through the decomposing lactose (61). As shown in Fig. 5, the outlet tube (2-cm in diameter) could easily be taken out, and the pyrolyzates collected in its inner walls were conveniently washed down with water. N,N-Dimethylformamide was used as the solvent for the acetonation of the purified pyrolyzates which were found in this research to be insoluble in acetone. The 1,6-anhydro-β-D-galactopyranose present in the pyrolyzates was acetonated with 2,2-dimethoxypropane using p-toluenesulfonic acid as the catalyst (62-64). It was through such modification that we were able to isolate 1,6-anhydro-3,4-O-isopropylidene-β-D-galactose (XI) (20 g, 18%) from α-lactose monohydrate (200 g). This yield, which is comparable to that reported by Hann and Hudson (60), was readily reproducible. The ease of reproduction is probably related mainly to the consistently forcing conditions used for acetonation, which perhaps in our hands were not achieved when using the procedure prescribed by Hann and Hudson (60).

Recently, Heyns and co-workers (93) analyzed the volatile products from the thermal degradation of D-glucose at 300°. The most volatile compounds were separated by repeated gas-liquid chromatography. Fifty six compounds were characterized by mass spectrometry, and confirmed by comparison with synthetic standard substances. In view of this result, the pyrolysis of a disaccharide

would be expected to give even more products. Thus, it seems unlikely that the yield (~18%) of 1,6-anhydro-3,4-O-isopropylidene-β-D-galactose (XI), which was obtained through the pyrolysis of α-lactose monohydrate, can be substantially improved. The economy in price of the starting material combined with the simplicity and speed of the experimental procedure, make up for the relatively low yield in the provision, by way of this modified procedure, of an abundant supply of 1,6-anhydro-3,4-O-isopropylidene-β-D-galactose (XI).

The n.m.r. spectra of 1,6-anhydro-3,4-O-isopropylidene-β-D-galactose (XI) (Fig. 4) and of its 2-O-acetyl derivative (XIIa) (Fig. 6) are noteworthy. For compound XI, the broad signal at τ7.29 was assigned to the hydroxyl proton since it disappeared when the $CDCl_3$ solution was shaken with D_2O. After the exchange, the signal for H-2 at τ6.14 became a well resolved doublet with a spacing of 1.0 Hz; therefore, there must be a slight coupling of the hydroxyl proton with H-2. Irradiation at the resonance frequency of H-1 (τ4.64) collapsed the doublet for H-2 (τ6.14), changed the form of the signal for H-3 (τ~5.79) and sharpened the signals for H-6' (τ 5.87) and H-6 (τ6.42). Irradiation at the resonance frequency of H-2 (τ6.14) changed the signal for H-1 into a well resolved doublet with $J_{1,3} = 1.2$ Hz. The signal for H-1 was found not to be a simple quartet resulting from coupling with H-2 and

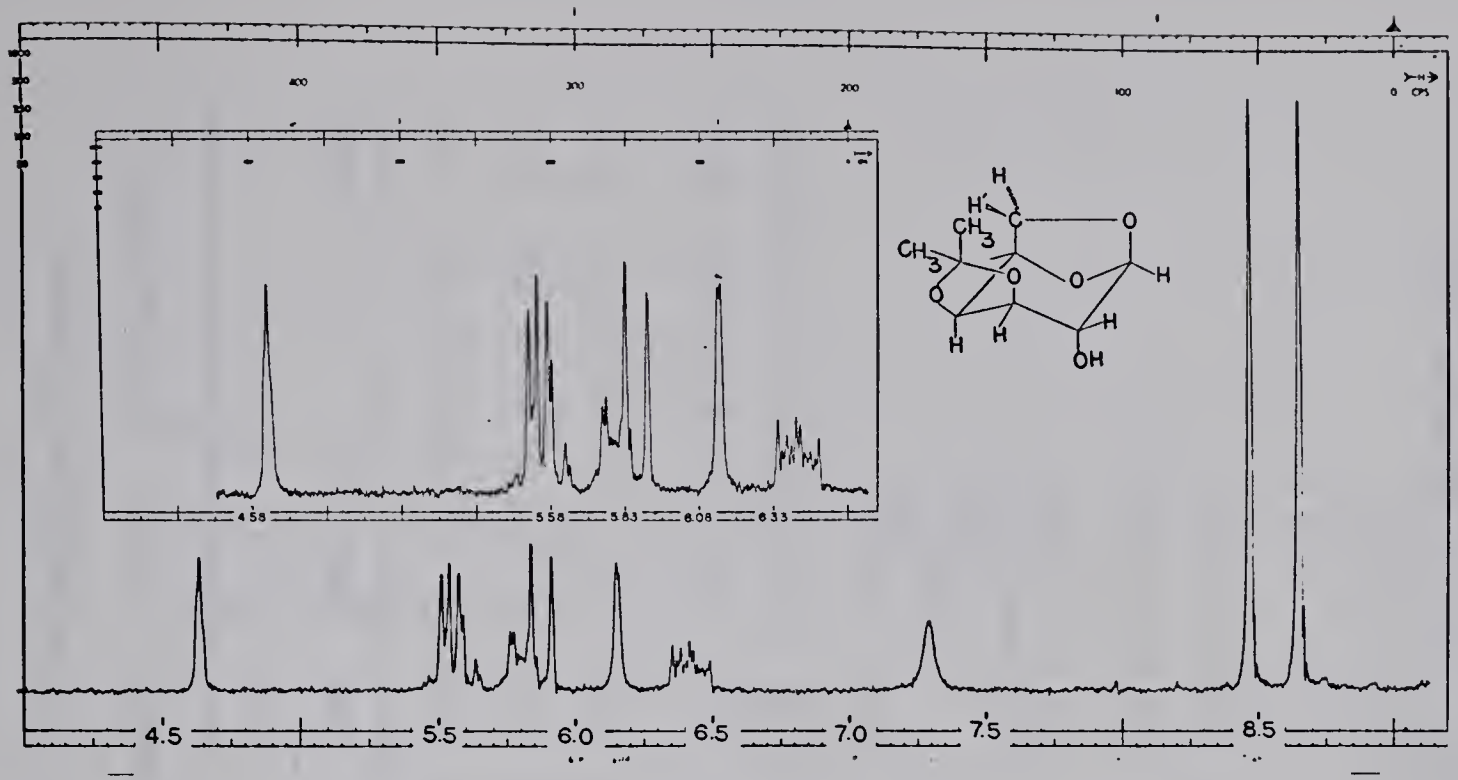


Fig. 4. N.m.r. spectrum (100 MHz) of 1,6-anhydro-3,4-O-isopropylidene-β-D-galactose (XI) ($CDCl_3$).

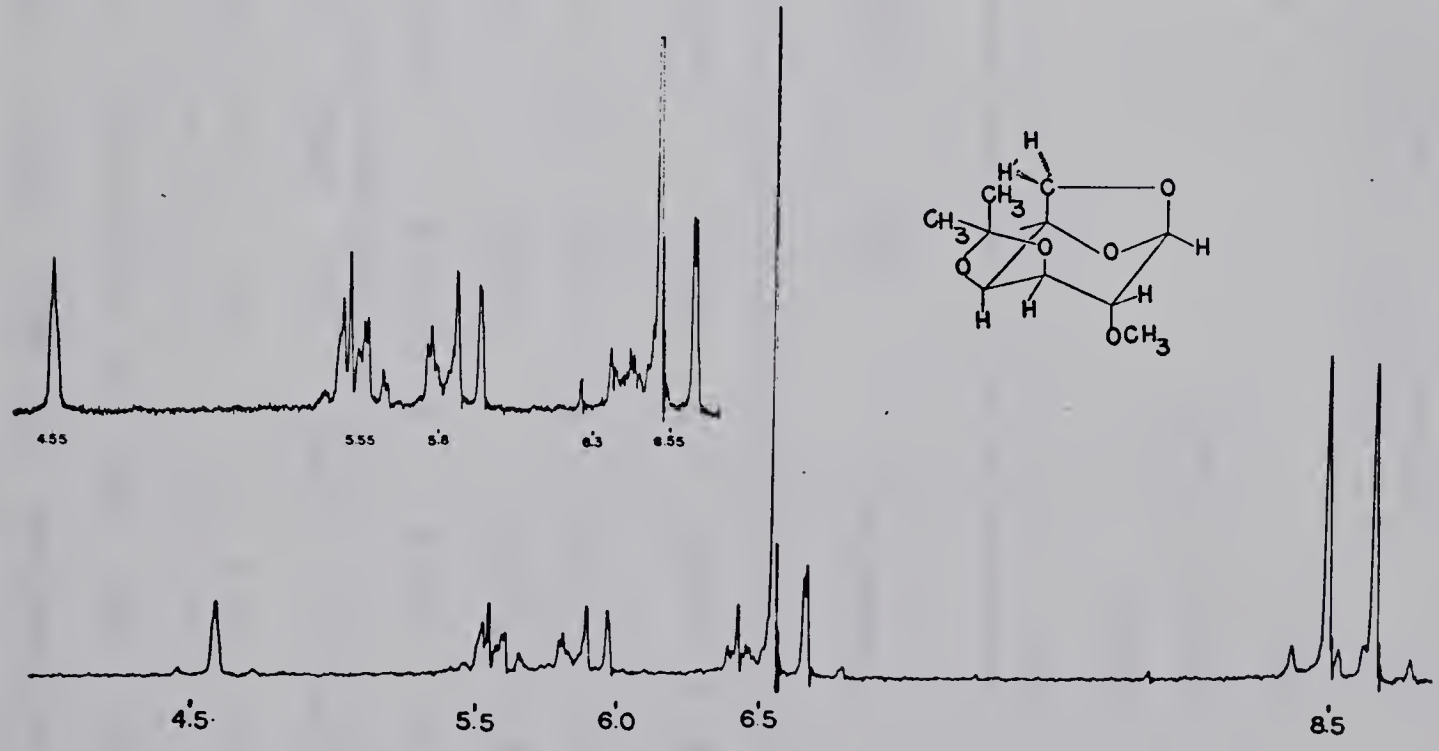


Fig. 7. N.m.r spectrum (100 MHz) of 1,6-anhydro-3,4-O-isopropylidene-2-O-methyl-β-D-galactose (XII) ($CDCl_3$).



Table IV

N.m.r. parameters (100 MHz, $CDCl_3$) of 1,6-anhydro-3,4-O-isopropylidene-β-D-galactose (XI) and its 2-O-acetyl (XIIa) and 2-O-methyl (XII) derivatives

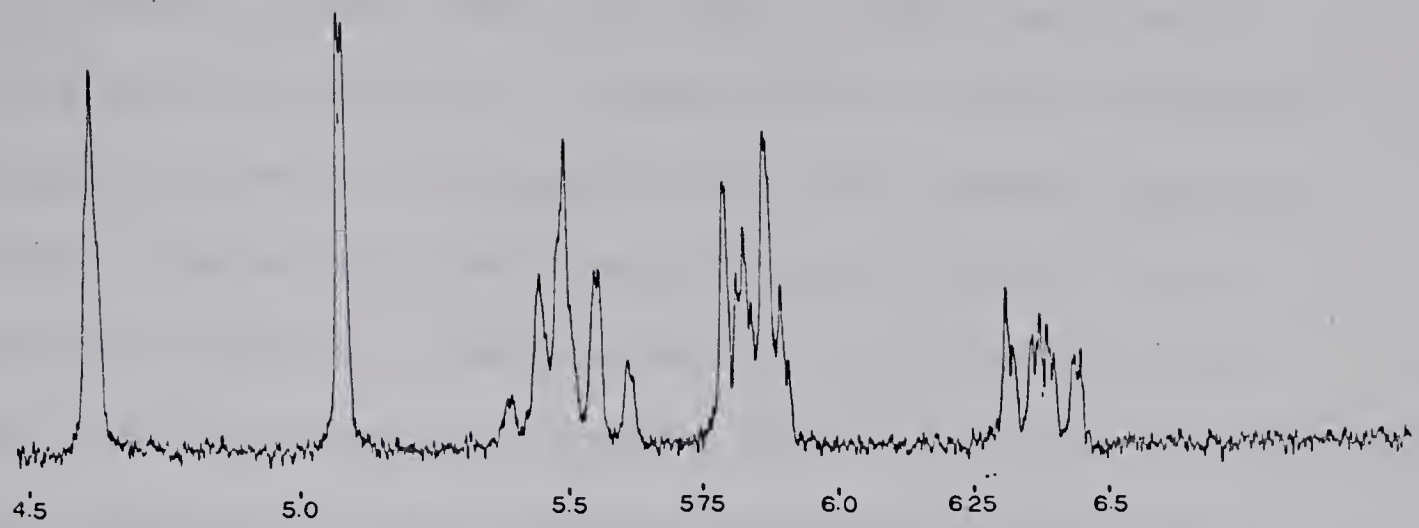
Compound	H-1 (τ)	$J_{1,2}$ (Hz)	H-2 (τ)	$J_{1,3}$ (Hz)	H-3 (τ)	$J_{3,4}$ (Hz)	H-4 (τ)	$J_{4,6}$ (Hz)	H-5 (τ)	$J_{5,6}$ (Hz)	$J_{5,6'}$ (Hz)	H-6' (τ)	H-6 (τ)	$J_{6,6'}$ (Hz)
XI	4.64	1.0	6.14	1.2	~5.79	-	~5.58	-	~5.54	6.2	0.5	5.87	6.42	7.5
XIIa	4.63	1.0	5.09	-	5.86	—	5.54	1.2	5.54	6.2	0.5	5.83	6.41	7.5
XIIa in pyd_5	4.32	1.0	4.79	$1.4 \approx J_{3,5}$	5.60	7.0	5.39	1.2	5.28	6.2	0.5	5.71	6.37	7.5
XII	4.58	0.9	6.65	1.2	~5.82	-	~5.50	-	~5.59	6.2	0.5	5.92	6.44	7.5

Compound	τ			
	OH	OCH_3	OAc	CH_3, CH_3
XI	7.29	-	-	8.46, 8.64
XIIa	-	-	7.86	8.43, 8.63
XIIa in pyd_5	-	-	7.96	8.46, 8.67
XII	-	6.52	-	8.46, 8.63

XI 1,6-anhydro-3,4-O-isopropylidene-β-D-galactose
XIIa 2-O-acetyl-1,6-anhydro-3,4-O-isopropylidene-β-D-galactose
XII 1,6-anhydro-3,4-O-isopropylidene-2-O-methyl-β-D-galactose

long-range coupling with H-3 ("W" conformation) (103-107), but exhibited additional multiplicity indicative of long-range coupling with H-6 (exo) ("W" conformation across the oxygen atom of the anhydro bridge) and H-6' (endo). The coupling constant of H-6' (endo) with H-5 was very small ($J_{5,6'} = 0.5$ Hz). This is as would be anticipated for a dihedral angle between H-5 and H-6' (endo) of approximately 90° as is to be expected from a consideration of a molecular model. By comparison with the n.m.r. spectrum of the 2-O-acetyl derivative (XIIa) (Fig. 6) in which the signals for H-3 was at τ 5.86, H-6' at τ 5.83 and H-5 at τ 5.54, the signal at about τ 5.79 was assigned to H-3.

Compound XI was acetylated with acetic anhydride in the presence of pyridine to yield crystalline 2-O-acetyl-1,6-anhydro-3,4-O-isopropylidene-β-D-galactose (XIIa) (60). Recrystallization from 50 parts of boiling water afforded pure material; m.p. 136-137°, $[\alpha]_D$ -51° (c, 0.88 in chloroform). The n.m.r. spectrum of this compound is shown in Fig. 6. The signal centered at τ6.41, doublets of a quartet, was assigned to H-6; large geminal coupling with H-6' ($J_{6,6'}$=7.5 Hz) and vicinal coupling with H-5 ($J_{5,6}$ = 6.2 Hz) produced the main quartet which was split further by long-range coupling with H-4 ($J_{4,6}$ = 1.2 Hz) ("W" conformation). Since the signal for H-6 was sharpened when irradiation was applied at the resonance frequency



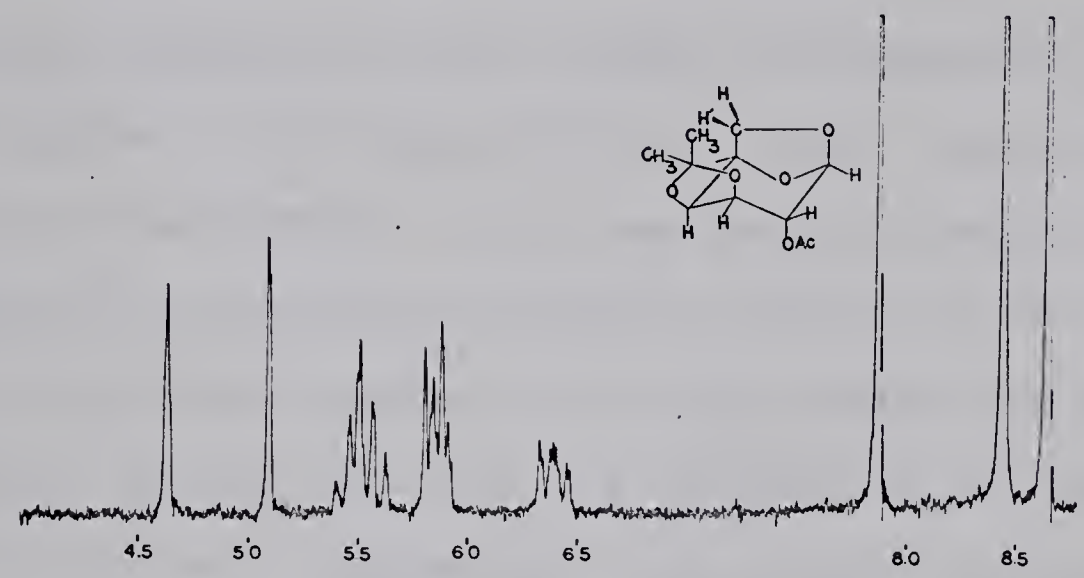


Fig. 6. N.m.r. spectrum (100 MHz) of 2-O-acetyl-1,6-anhydro-3,4-O-isopropylidene-β-D-galactose (XIIa) ($CDCl_3$).

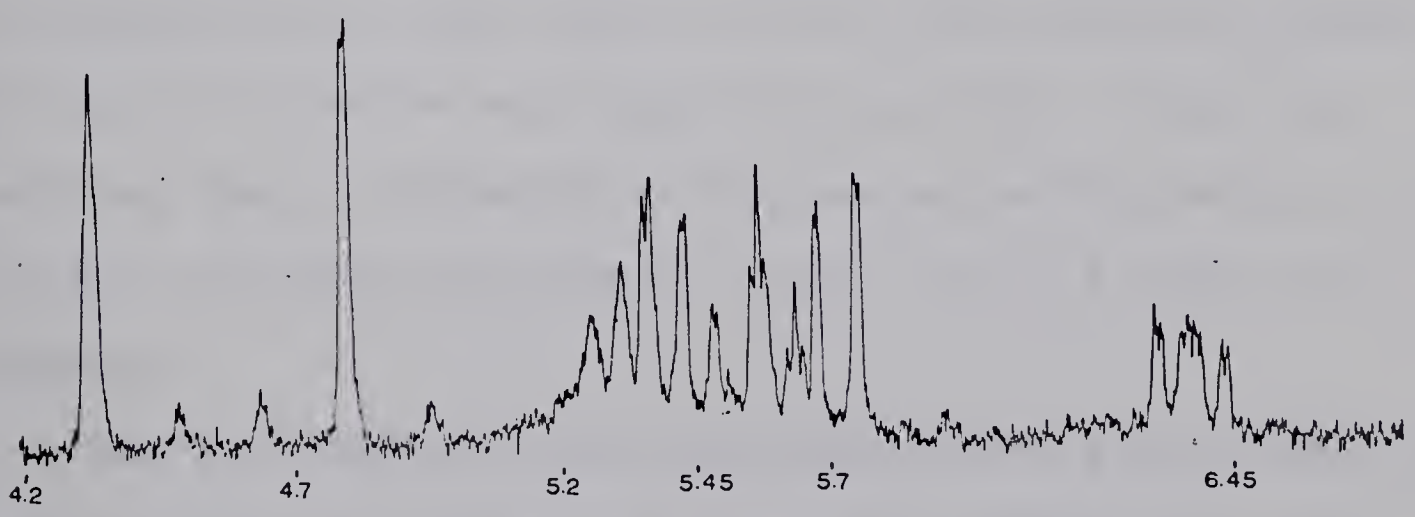


Fig. 6. N.m.r. spectrum (100 MHz) of 2-O-acetyl-1,6-anhydro-3,4-O-isopropylidene-β-D-galactose (XIIa)(pyridine-d_5).

of H-1 (τ4.63), there must also be a slight long-range coupling of H-6 with H-1. Irradiation at τ5.54 collapsed the signal for H-6 to a doublet with the largest spacing (7.5 Hz). Therefore, the signals for H-4 and H-5 must be at this position. The quartet at τ5.83 was assigned to H-6', with the smaller spacing (0.5 Hz) assigned to the vicinal coupling of H-6' with H-5. Irradiation at the resonance frequency of H-6 (τ6.41) collapsed this quartet to a singlet. The signal for H-3 (τ5.86) appeared to be triplets of a doublet. This was readily observed when pyridine-d_5 was used as solvent in which H-3 (now at τ5.60) was well shifted chemically from the signal for H-6'. The large spacing (7.0 Hz) was assigned to the coupling of H-3 with H-4. Long-range coupling of 1,3-diequatorial protons ("W" conformation) is possible with H-1 and H-5, to give the observed splitting of each principal line in the H-3 signal into triplets ($J_{1,3} = J_{3,5} = 1.4$ Hz). From the appearance of the signal for H-3, the coupling between H-2 and H-3 must be very small ($J_{2,3} \simeq 0$ Hz). This was verified when irradiation at the resonance frequency of H-1 (τ4.63) collapsed the doublet of H-2 ($J_{1,2} = 1.0$ Hz) to a singlet.

For 1,6-anhydro-3,4-O-isopropylidene-β-D-galactose (XI) (Fig. 4) and its 2-O-acetyl derivative (XIIa) (Fig. 6), it is interesting to note that the vicinal coupling constants are in agreement with the Karplus relationship(100, 101).

From examination of a molecular model, the dihedral angles between H-5 and H-6, and that of H-5 and H-6' are estimated to be approximately 30 and 90° which correspond to coupling constants of 6.0 and 0 Hz respectively. Indeed, the following values were found: $J_{5,6}=6.2$ Hz and $J_{5,6'}=0.5$. The 3,4-O-isopropylidene group must have slightly flattened the pyranose ring and decreased the dihedral angle defined by H-3 and H-4 from 45 to 20° to give the observed value for $J_{3,4}=7.0$ Hz. Since $J_{2,3}$ was very small ($J_{2,3}\simeq 0$ Hz), the dihedral angle defined by H-2 and H-3 must be distorted and approached 90°. Another interesting feature found in these two spectra (Fig. 4 and 6) is the presence of long-range couplings between equatorial protons separated by four bonds ("W" conformation) (103-107). The following values were obtained: $J_{1,3}=J_{4,6}=1.2$ Hz and $J_{3,5}=1.4$ Hz. It is also interesting to note that the geminal coupling between H-6 and H-6' ($J_{6,6'}=7.5$ Hz) is smaller than what would be expected (12-15 Hz) (102).

The second stage in the synthesis of 2-O-acetyl-β-noviose (XXV) (Fig. 37) involved the methylation of compound XI, using sodium hydride-methyl iodide, to 1,6-anhydro-3,4-O-isopropylidene-2-O-methyl-β-D-galactose (XII) in 98% yield. Other workers (67, 68) have reported this methylation procedure to be superior to either those of Purdie (108) or of Haworth (65). 1,6-Anhydro-3,4-O-isopropylidene-2-O-methyl-β-D-galactose (XII) was obtained

in crystalline state for the first time.

The n.m.r. spectrum of compound XII is shown in Fig. 7. The doublet with a spacing of 0.9 Hz at the highest field (τ6.65) was assigned to H-2. Irradiation at the resonance frequency of H-1 (τ4.58) collapsed this doublet, changed the character of the H-3 signal (τ5.82) and sharpened the signals for H-6' (τ5.92) and H-6 (τ6.44). Irradiation at the resonance frequency of H-2 (τ6.65) changed the signal for H-1 into a well resolved doublet with $J_{1,3}$ =1.2 Hz and also changed the feature for H-3 (τ5.82). The signal for H-1 was found not to be a simple quartet for reasons which were mentioned earlier.

The third stage in the synthetic scheme (Fig. 37) was to hydrolyze compound XII to 2-O-methyl-D-galactose. Mild hydrolysis with acid of 1,6-anhydro-3,4-O-isopropylidene-2-O-methyl-β-D-galactose (XII) has been reported (61) to remove the O-isopropylidene group to give 1,6-anhydro-2-O-methyl-β-D-galactopyranose in high yield. This intermediate was not required for our purpose and compound XII was subjected to hydrolysis under more vigorous conditions (66) to provide 2-O-methyl-β-D-galactopyranose (XIII) which was isolated in the crystalline state. Compound XIII could also be prepared from methyl galactopyranosides (109, 110).

Recently 1,3,4,6-tetra-O-acetyl-α-D-galactopyranose (111, 140) was methylated with diazomethane and boron

trifluoride etherate (112) without acetyl migration to give 1,3,4,6-tetra-O-acetyl-2-O-methyl-α-D-galactopyranose in high yield (70-90%). Deacetylation of the latter compound with sodium methoxide in methanol gave 2-O-methyl-β-D-galactopyranose (XIII) in yield of about 80%. Helferich and Zirner (111) prepared the starting material 1,3,4,6-tetra-O-acetyl-α-D-galactopyranose by hydrolysis of tetra-O-acetyl-α-D-galactopyranosyl bromide, analogous to the procedure used for the preparation of 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose. Recently, Detert (140) prepared 1,3,4,6-tetra-O-acetyl-α-D-galactopyranose by hydrolysis of tri-O-acetyl-1,2-O-(1'-ethoxyethylidene)-α-D-galactopyranose with 95% aqueous acetic acid as well as by hydrogenolysis of tri-O-acetyl-1,2-O-(1'-benzyloxyethylidene)-α-D-galactopyranose in 86% yield in both methods. Since the 1,2-orthoesters of D-galactopyranose can be obtained in high yields (140), this alternative route of obtaining 2-O-methyl-β-D-galactopyranose (XIII) via 1,3,4,6-tetra-O-acetyl-α-D-galactopyranose appears attractive.

The n.m.r. spectrum of crystalline 2-O-methyl-β-D-galactopyranose (XIII) in deuterium oxide after 27 h is shown in Fig. 8. The procedure used here was to dissolve the sugar in deuterium oxide and to determine the n.m.r. spectrum on the Varian A60 spectrometer with tetramethylsilane as the external standard. The 100 MHz

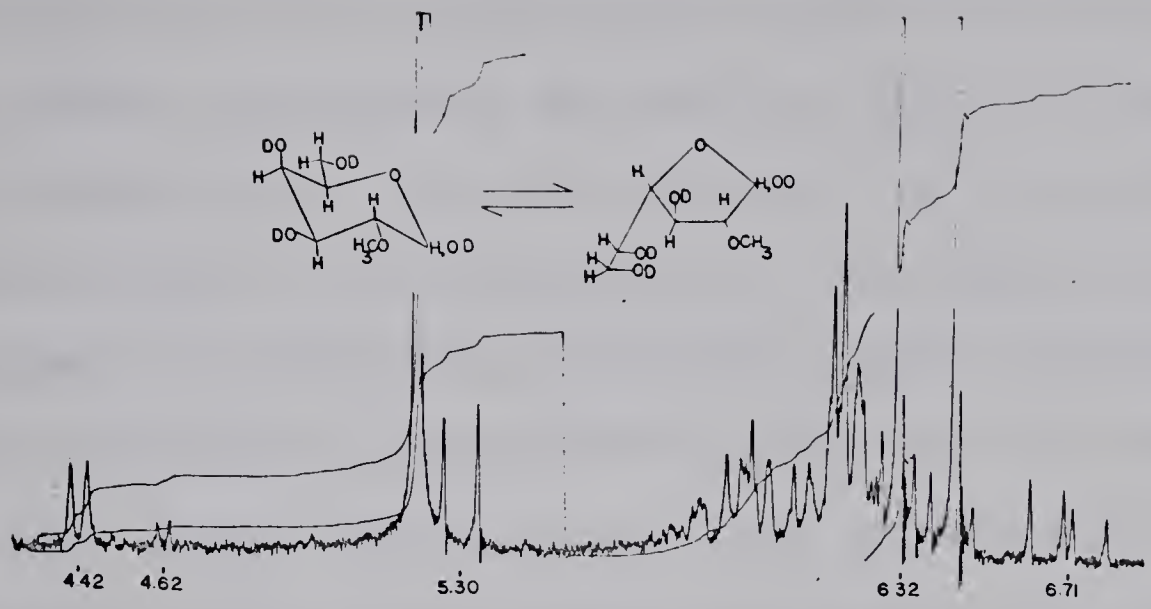


Fig. 8. N.m.r. spectrum (100 MHz) of 2-O-methyl-D-galactose (D_2O).

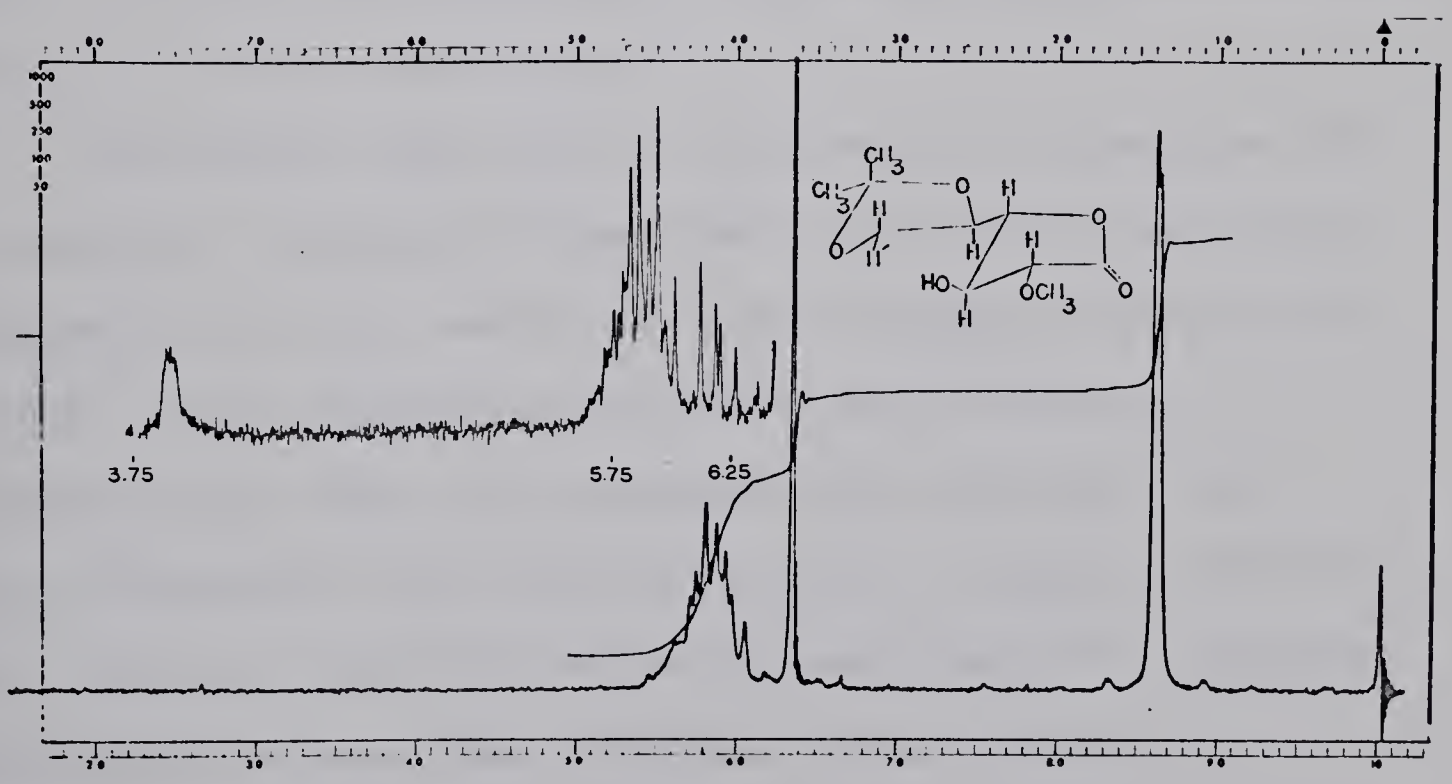


Fig. 9. N.m.r. spectrum (60 MHz) of 5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XV) ($CDCl_3$). Inset (100 MHz) (DMSO-d_6).

spectrum of the solution after 27 h was measured. The line positions were established relative to calibration side bands and placed on the scale as tau (τ) values from tetramethylsilane using the positions for the anomeric protons found in the A60 spectrum. The crystalline compound was indeed in the β-D form, since, immediately after dissolution, the anomeric proton (τ5.30) seemed to be axial, being coupled to H-2 to an extent (8 Hz) consistent with an axial-axial arrangement. The spectrum of the solution at equilibrium also revealed two other doublets at lower field (τ4.42 and 4.62) which belong to the anomeric protons of 2-O-methyl-α-D-galactopyranose ($J^{\alpha}_{1,2} = 3.8$ Hz) and possibly a 2-O-methyl-D-galactofuranose ($J_{1,2} = 2.8$ Hz) respectively.

Generally, when one of the anomers of furanoses has a coupling constant of less than 1 Hz, it can be safely assumed that this anomer has the 1,2-trans configuration (143). This conclusion follows from the Karplus relationship (100, 101) together with the fact that, on a 5-membered ring, the H-1 and H-2 in cis relationship must define a dihedral angle of less than 50°. Coupling constants of less than 3 Hz most likely indicate a 1,2-trans relationship. Therefore, the signal at τ4.62 probably belongs to 2-O-methyl-β-D-galactofuranose with $J^{\beta'}_{1,2} = 2.8$ Hz. This would agree with the general expectation that the 1,2-trans-β configuration provides the more stable

anomer in aqueous solution. It can also be concluded that the concentrations of the other furanose form and the open-chain form (if any) were too low to be observed by n.m.r.

Integration of the anomeric signals showed that the mixture at equilibrium at room temperature contained 48% 2-O-methyl-β-D-galactopyranose (XIII), 42% 2-O-methyl-α-D-galactopyranose and 10% 2-O-methyl-β-D-galactofuranose.

Irradiation of H_1^β (τ5.30) caused the quartet centered at τ6.71 to collapse to a doublet. Therefore the chemical shift for H_2^β ≃τ6.71 and $J_{2,3}^\beta$ ≃10 Hz. The shape of the signal for H_1^α (τ4.42) showed the presence of second-order effects from virtual long-range coupling and, therefore, a small chemical shift for H_2^α and H_3^α (113, 114). Irradiation of H_1^α caused the quartet centerd at τ6.42 to collapse to a doublet. Therefore the signal for H_2^α was at this position and $J_{2,3}^\alpha$ ≃10 Hz. The spacings observed in the spectrum for 2-O-methyl-β-D-galactopyranose (XIII) (see Table V) indicate that the compound exists in a near C-1 chair conformation.

Following the scheme for the synthesis of 2-O-acetyl-β-noviose (XXV) in Fig. 37, the next stage required oxidation of compound XIII to 2-O-methyl-D-galactono-1,4-lactone (XIV). This was achieved in a near quantitative yield with bromine water using barium benzoate dihydrate (69) as a buffer. Bunzel and

Table V

N.m.r. parameters (100 MHz, D_2O) of

2-O-methyl-D-galactose

Compound	H-1 (τ)	$J_{1,2}$ (Hz)	H-2 (τ)	$J_{2,3}$ (Hz)	O-CH_3 (τ)
2-O-methyl-β-D-galactopyranose	5.30	8	6.71	10	6.32
2-O-methyl-α-D-galactopyranose	4.42	3.8	6.42	10	6.45
2-O-methyl-β-D-galactofuranose	4.62	2.8	--	--	--

Matthews (115) have shown that free bromine is the active oxidant and that neither hypobromous acid nor tribromide ions are significant oxidants under the conditions used. The rate of oxidation is inversely proportional to the acidity (115). Isbell and co-workers (116, 117) showed that δ-lactones were the primary oxidation products in buffered, slightly acid solution for the α- and β-anomers of several sugars. They also showed that, for thirteen sugars, the β-anomer was always oxidized faster than the α-form (118). Generally, the oxidation of the β-anomers was too fast for concurrent transformation into α-anomers to be significant, but this was not so with the α-anomers (119). Overend and co-workers (119) found that even with a ten-fold excess of bromine, "direct" oxidation of the α-form was only a minor reaction, most of the oxidation proceeding through the β-anomers. A 45-fold molar excess of bromine would be

required to make the rate of direct oxidation equal to the rate of anomerization, in the aqueous acetate buffer of pH 5. Increasing the initial concentration of bromine increases the proportion of direct oxidation at the expense of anomerization. They also found that the oxidation was not first-order in β-D-glucopyranose. Even in the presence of a large excess of bromine the rate coefficients fell sharply as the reaction proceeded. This trend was not caused by the conversion of free bromine into tribromide ions because, although this did occur, its effect upon the rate was too small, as was shown by comparable experiments with cyclohexanol (120). With this alcohol there was no change in rate coefficients when a ten-fold excess of bromine was used. Nor was the retardation due to the conversion of the β-form into the much less readily oxidized α-D-glucopyranose, since β-D-glucopyranose was oxidized about 45 times faster by a ten-fold excess of bromine than it anomerized in the acetate buffer, pH 5. They calculated that, under these conditions, β-D-glucopyranose was oxidized by bromine water at least 250 times faster than was α-D-glucopyranose.

It is well known that D-galactose in aqueous solution behaves differently from D-glucose. The mutarotation of D-glucose follows the first-order equation and is represented as follows:

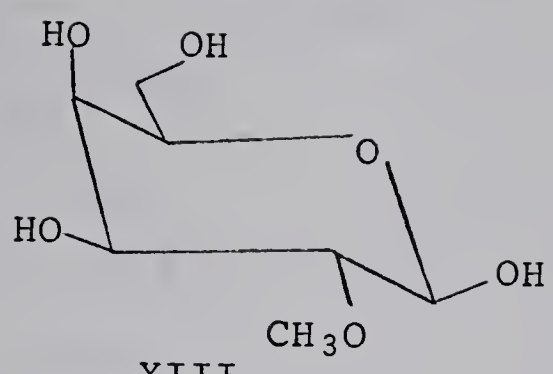
$$\alpha \underset{K_2}{\overset{K_1}{\rightleftharpoons}} \beta \qquad \text{(a)}$$

$$-\frac{d\alpha}{dt} = K_1[\alpha] - K_2[\beta] \qquad \text{(b)}$$

Equation (b) gives the rate of change of the α- into the β-form at the time t. The reaction constant for α → β is K_1, and for β → α is K_2. The concentrations of the α- and β-form at the time t are represented by [α] and [β].

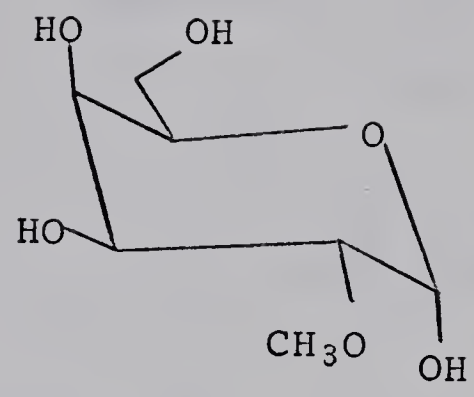
However, D-galactose exhibits mutarotation which does not follow the first-order equation and, therefore, the equilibrated solution must have an appreciable quantity of at least one other isomer besides the pyranose forms. Galactose is known to exist in nature as furanosides as well as pyranosides. This is probably related to the inherently favorable configuration (all trans) of this compound in the furanose-ring form. However, the furanose forms could not be detected by n.m.r. (114) when D-galactose was dissolved in D_2O at equilibrium. On the other hand, an equilibrated solution of 2-O-methyl-D-galactose revealed the presence of 2-O-methyl-β-D-galactofuranose to the extent of 10% by n.m.r. (see Fig. 8).

Since 2-O-methyl-β-D-galactofuranose is present in a significant concentration (10%) at equilibrium, the formation of 2-O-methyl-D-galactono-1,4-lactone (XIV) may arise directly from the furanose or follow the analogous pathway as β-D-glucopyranose (119, 121). The mechanism is outlined in Fig. 40.

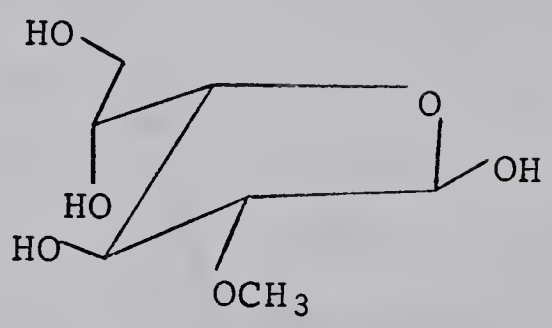


XIII

48%



42%



OCH_3

10%

Following the proposals made by Isbell (116, 117) and later by other authors (119, 121), the conjugate acid of the hypobromite ester (1) was first formed from the 2-O-methyl-β-D-galactopyranose (XIII) and bromine, and lost a proton to form the hypobromite (2). This hypobromite (2) then readily underwent elimination of hydrogen bromide to yield the δ-lactone (3). This mechanism explains the large difference in the reactivity of the α- and β-anomers

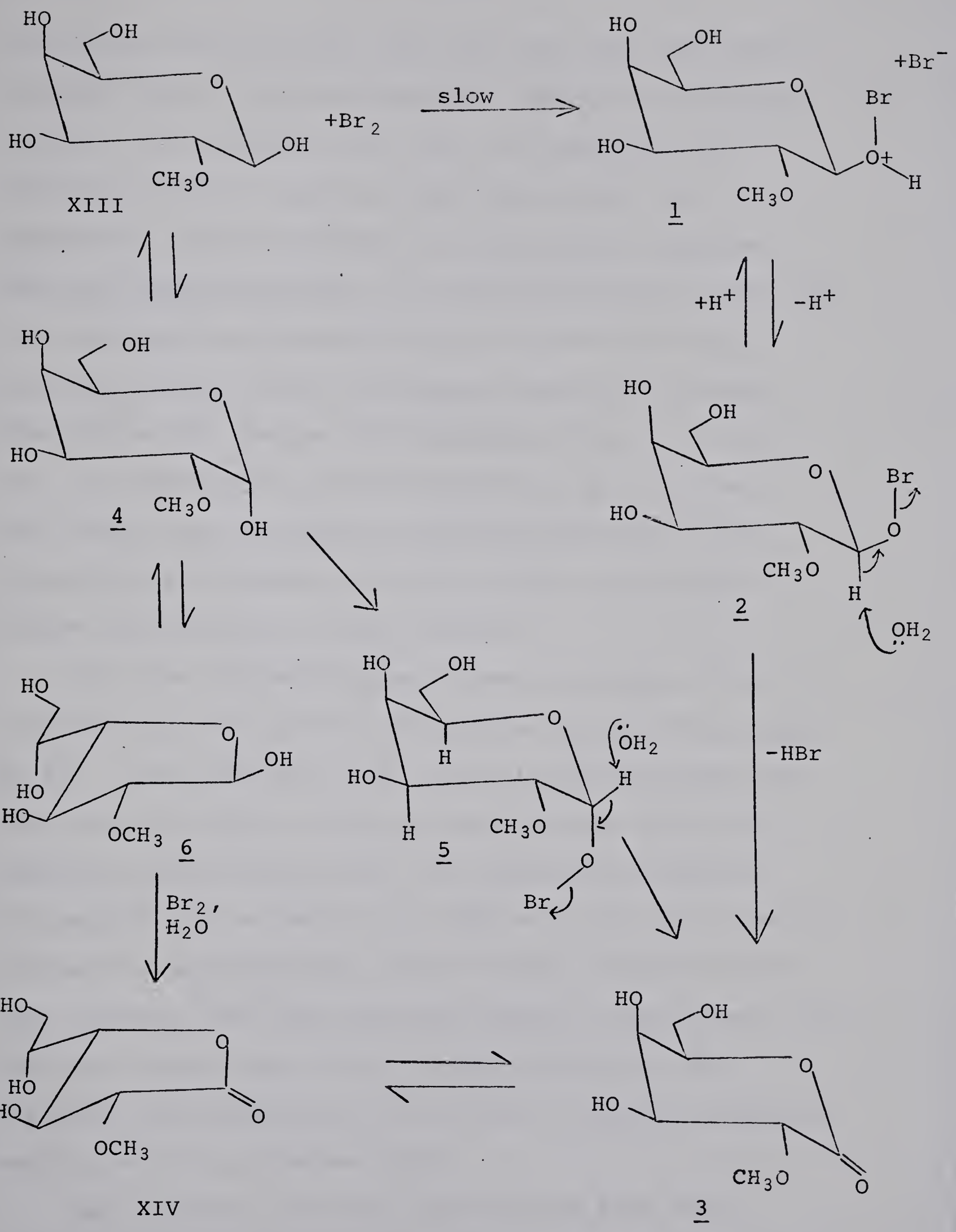


Fig. 40. Mechanism for the formation of 2-O-methyl-D-galactono-1,4-lactone (XIV).

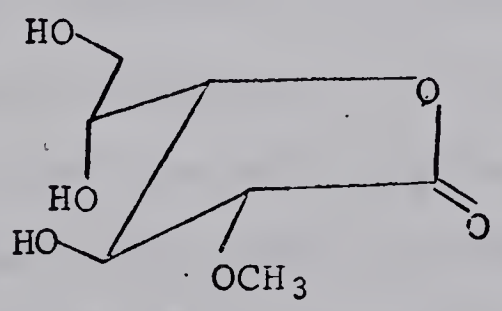
(118) very satisfactorily, for, not only does the bromine molecule attack the more accessible equatorially hydroxyl group in the β-D-anomer, but the 1,2-elimination of hydrogen bromide is greatly facilitated since the hypobromite group can adopt the configuration required for the trans-elimination. In the case of the α-isomer (4), the corresponding hypobromite (5) is relatively highly strained because of the non-bonded interactions between the bromine and the two axial hydrogen atoms at C-3 and C-5. If 2-O-methyl-β-D-galactofuranose (6) is oxidized much faster than 2-O-methyl-β-D-galactopyranose (XIII), 2-O-methyl-D-galactono-1,4-lactone (XIV) is expected to be the first product of the reaction.

Only the 2-O-methyl-D-galactono-1,4-lactone (XIV) was isolated when the aqueous solution was evaporated *in vacuo* at 50°. The γ-lactone (XIV) is easily distinguished from the δ-lactone both by infrared spectroscopy (123) and optical rotation (124, 125). The stretching frequency of compound XIV is found to be 1788 cm^{-1}; for the δ-lactone, it would be approximately 1735 cm^{-1} (126). The fact that the γ-lactone (XIV) was isolated readily in high yield (97%) does not require that it was formed directly in the oxidation since galactono-1,5-lactone is known to isomerize readily to the 1,4-lactone (122).

The "lactone rule" in its qualitative form (124) stipulates that a lactone is more dextrorotatory than the

free acid if the hydroxyl group involved in lactone formation has the D-configuration. Since the optical rotation of the isolated crystalline D-galacto-compound XIV is -63° and increased to -26° after 224 h at room temperature, it must be the γ-lactone. The δ-lactone would have a positive rotation (124, 125). The fact that the optical rotation increased from -63° to -26° after 224 h at room temperature indicates that the γ-lactone (XIV) in aqueous solution was converted in part to the corresponding δ-lactone and the free acid.

The almost exclusive existence of 2-O-methyl-D-galactonolactone as the γ-lactone (XIV) on isolation should not be too surprising, since the 2-, 3- and 4-substituents of compound XIV are all in the trans-equatorial relationship, and the $-O-\overset{|}{C}=O$ group conforms well to the envelope conformation shown should the C_1-O bond possess double-bond character. It is also well known that γ-lactones in general are more stable than δ-lactones (122).



XIV

This is in accordance with the generalization of Brown, Brewster and Shechter (127) which states that "reactions will proceed in such a manner as to favor the formation or retention of the exo double bond in the 5-membered ring and to avoid the formation or retention of the exo double bond in the 6-membered ring systems". Lemieux has discussed this point in detail (128).

The next stage in the synthesis of 2-O-acetyl-β-noviose (XXV) (Fig. 37) required the acetonation of 2-O-methyl-D-galactono-1,4-lactone (XIV) to give 5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XV). This was achieved in high yield (90%) by reacting compound XIV with 2,2-dimethoxypropane in 1,2-dimethoxyethane using p-toluenesulfonic acid as the catalyst. Evans and co-workers (63) have shown that the equilibrium in cyclic ketal formation from 2,2-dimethoxypropane is thermodynamically favorable unless the cyclic ketal is highly strained Although the reaction could be expected to proceed directly from the 2,2-dimethoxypropane, Hampton (131) has suggested that acetone is the primary reactant and that the 2,2-dimethoxypropane acts mainly as a desiccant.

The n.m.r. spectrum of 5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XV) is shown in Fig. 9. The 60 MHz spectrum in $CDCl_3$ revealed the methoxyl signal at τ 6.35 and the two geminal C-methyl signals at τ8.60 and 8.64. The signals of the remaining protons are bunched together

between τ5.44 and 6.05. The signal of the hydroxyl proton was shifted down-field and could be observed well when DMSO-d_6 was used as solvent. The 100 MHz spectrum of this solution is shown in Fig. 9. The hydroxyl proton appeared as a broad signal with fine splittings centered at τ3.91. The shape of this signal undoubtedly shows the presence of second-order effects from virtual long-range coupling. This suggests possibly that the chemical shifts of H-2, H-3 and H-4 are close to one another. Irradiation at the resonance frequency of the O-H (τ3.91) changed the feature of the signals in the region of τ5.83-5.90. Thus, it was likely that the signals for H-2, H-3 and H-4 were at this position. This was confirmed when the solution was shaken with D_2O causing the disappearance of the hydroxyl proton at τ3.91. The signal for H-6 now appeared as a quartet centered at τ6.20 with the larger spacing (8.3 Hz) assigned to the geminal coupling of H-6 with H-6', and the smaller spacing (6.3 Hz) assigned to the vicinal coupling of H-6 with H-5. Irradiation of each single peak for H-6 at [374.3 c.p.s.] and [380.4 c.p.s.] split the signals centered at τ5.95 and 5.73. Therefore, it was likely that the signal for H-6' was at τ5.95 with $J_{5,6'} \simeq 5.0$ Hz. The chemical shift of H-5 was at about τ5.73. Since irradiation at the position of the signal for the O-H (broad singlet at τ3.91) most seriously changed the signal at about τ5.90, the

Table VI

N.m.r. parameters (60 MHz, $CDCl_3$) and (100 MHz, DMSO-d_6) of 5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XV)

Compound XV in	H-2 (τ)	H-3 (τ)	H-4 (τ)	H-5 (τ)	H-6 (τ)	H-6' (τ)	$J_{5,6}$ (Hz)	$J_{5,6'}$ (Hz)	$J_{6,6'}$ (Hz)	O-H (τ)	$O-CH_3$ (τ)	$\diagup\!\!\diagdown^{CH_3}_{CH_3}$ (τ)
DMSO-d_6	~5.95	~5.90	~5.83	~5.73	6.20	5.95	6.3	5.0	8.3	3.91	6.50	8.71
$CDCl_3$	-	-	-	-	-	-	-	-	-	6.35	8.60, 8.64	

latter signal was assigned to H-3. By comparison with the n.m.r. spectrum of 3-O-acetyl-5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XVI), which is shown in Fig. 10, the chemical shifts of τ5.95 and 5.83 were assigned to H-2 and H-4, respectively.

The next stage in the synthesis of 2-O-acetyl-β-noviose (XXV) (Fig. 37) involved the introduction of two methyl groups on C-1 of compound XV or its derivatives. Attempts to react 5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XV) directly with methyl magnesium iodide in a mixture of ether-benzene or tetrahydrofuran were not successful. A copious precipitate was observed during the course of the reaction. The products upon isolation in the usual manner (see Experimental section VIII, 1) gave a streak on a thin-layer chromatogram. When compound XV in tetrahydrofuran was reacted with one equivalent of methyl lithium followed by an excess of methyl magnesium iodide, a copious precipitate was again observed. The isolated product did not even show the presence of a methoxyl signal in the n.m.r. spectrum.

The acetylated glyconolactones have been reported to react with Grignard reagents to produce tertiary alcohols (34). An excess of Grignard reagent is required to allow for full reaction at the acetyl groups. Thus a minimum of ten moles of Grignard reagent would be required per mole of tetraacetyl-D-gluconolactone, eight for the acetyl

groups and two for the lactone function. Hence, 3-O-acetyl-5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XVI) was prepared to investigate its usefulness in reaction with the Grignard reagent.

The n.m.r. spectrum of 3-O-acetyl-5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XVI) is shown in Fig. 10. The quartet integrating for one proton at the lowest field (τ4.61) was assigned to H-3 with the larger spacing (6.0 Hz) assigned to the coupling of H-3 with H-2, and the smaller spacing (5.0 Hz) assigned to the coupling of H-3 with H-4. Irradiation at this resonance frequency changed the nature of the signals centered at τ5.80 and 5.74. Therefore, the doublet at τ5.80 was assigned to H-2, and the quartet at τ5.74 assigned to H-4 with $J_{4,5} \simeq 3.5$ Hz. The signals for H-6 and H-6' appeared as an octet to a higher field than the signal for H-5 (τ5.60). Treating these three protons as an isolated ABX system, the following n.m.r. parameters were obtained, $\delta_A - \delta_B \simeq 0.18$ p.p.m., $J_{AB} \simeq 8.5$ Hz, $\delta_A - \delta_X \simeq 0.5$ p.p.m., $J_{AX} = 6.3$ Hz, $J_{BX} = 6.5$ Hz with δ_A at τ6.10. The observed coupling constants J_{AX} and J_{BX} were very similar. By comparison with the n.m.r. spectrum of 5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XV) shown in Fig. 9, the A-proton was assigned to H-6 and the B-proton to H-6'

When 3-O-acetyl-5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XVI) was reacted with 20 equivalents of methyl magnesium iodide in ether, 1-deoxy-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-D-galacto-heptitol (XX)

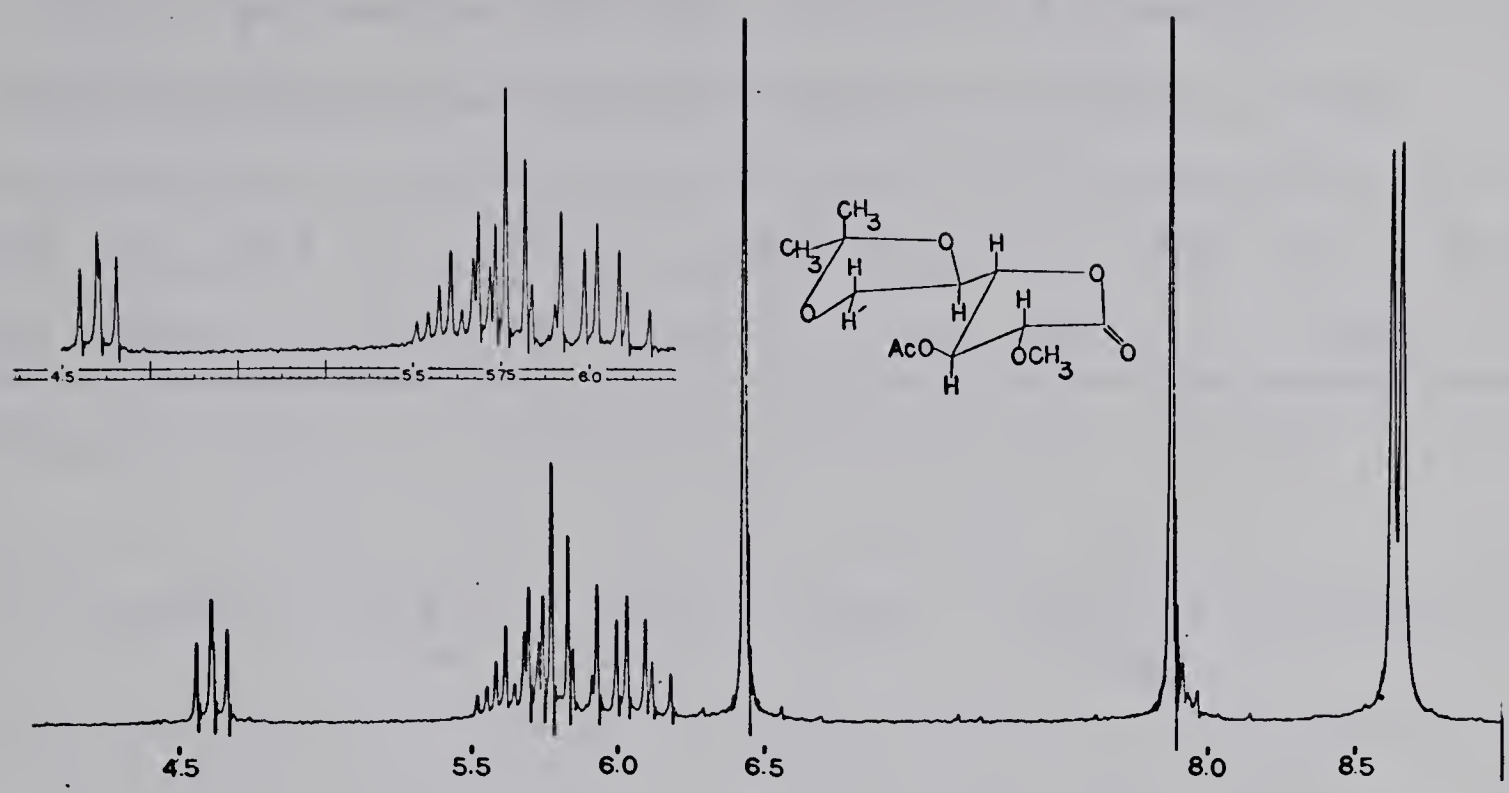


Fig. 10. N.m.r. spectrum (100 MHz) of 3-O-acetyl-5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XVI) ($CDCl_3$).

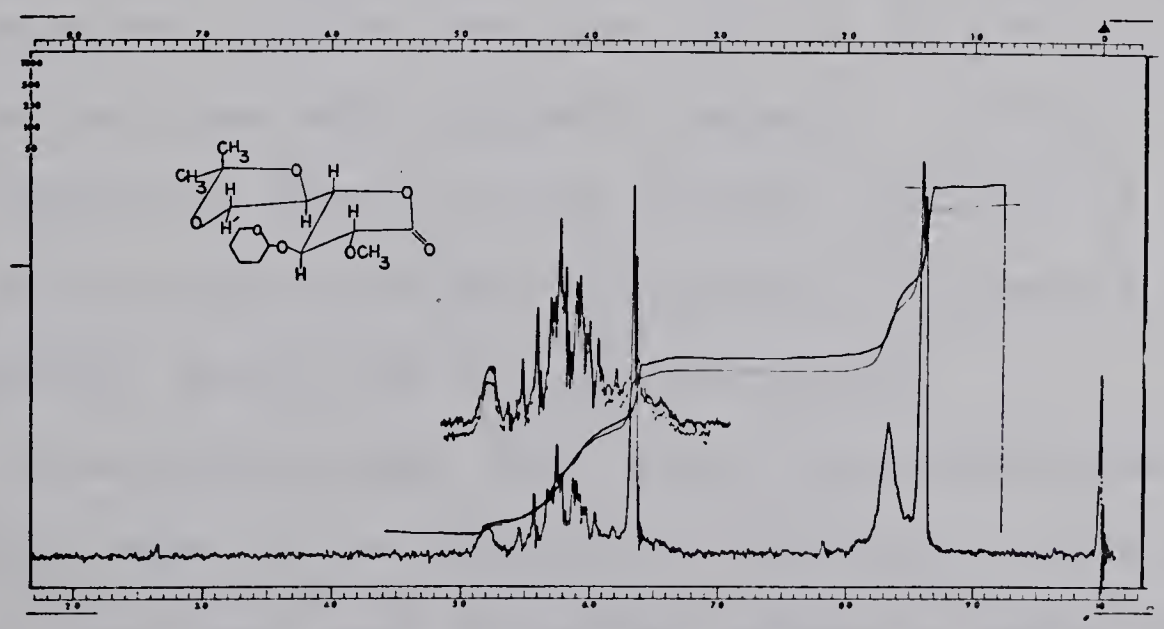


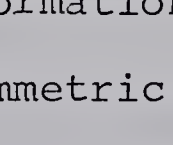
Fig. 11. N.m.r. spectrum (60 MHz) of 5,6-O-isopropylidene-2-O-methyl-3-O-tetrahydropyranyl-D-galactonolactone (XVII) ($CDCl_3$).



Table VII

N.m.r. parameters (100 MHz, $CDCl_3$) of 3-O-acetyl-5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XVI)

H-2 (τ)	$J_{2,3}$ (Hz)	H-3 (τ)	$J_{3,4}$ (Hz)	H-4 (τ)	$J_{4,5}$ (Hz)	H-5 (τ)	$J_{5,6}$ (Hz)	$J_{5,6'}$ (Hz)	H-6 (τ)	$J_{6,6'}$ (Hz)	H-6' (τ)
5.80	6.0	4.61	5.0	5.74	3.5	5.60	6.3	6.5	6.10	8.5	5.92

$-O-CH_3$ = τ6.43 -OAc = τ7.87  = τ8.62,8.65

was isolated as a colorless syrup in 36% yield. A certain amount of white precipitate could still be observed during the course of the reaction. Obviously, the yield of the reaction left much to be desired. Other workers(34) also reported poor yields from the reaction of acetylated glyconolactones with Grignard reagents. A search was made for protecting groups of the hydroxyl function of compound XV, which would allow the preparation of compound XX or a suitable dérivative in improved yields.

Tetrahydropyranyl (THP) ethers and other mixed acetals, made by the addition of alcohols to alkyl vinyl ethers have been used to protect alcohols against the action of Grignard reagents (72). The formation of mixed acetals involves the creation of an asymmetric center and, hence, with optically active alcohols, a mixture of diastereoisomeric acetals is usually formed, but this

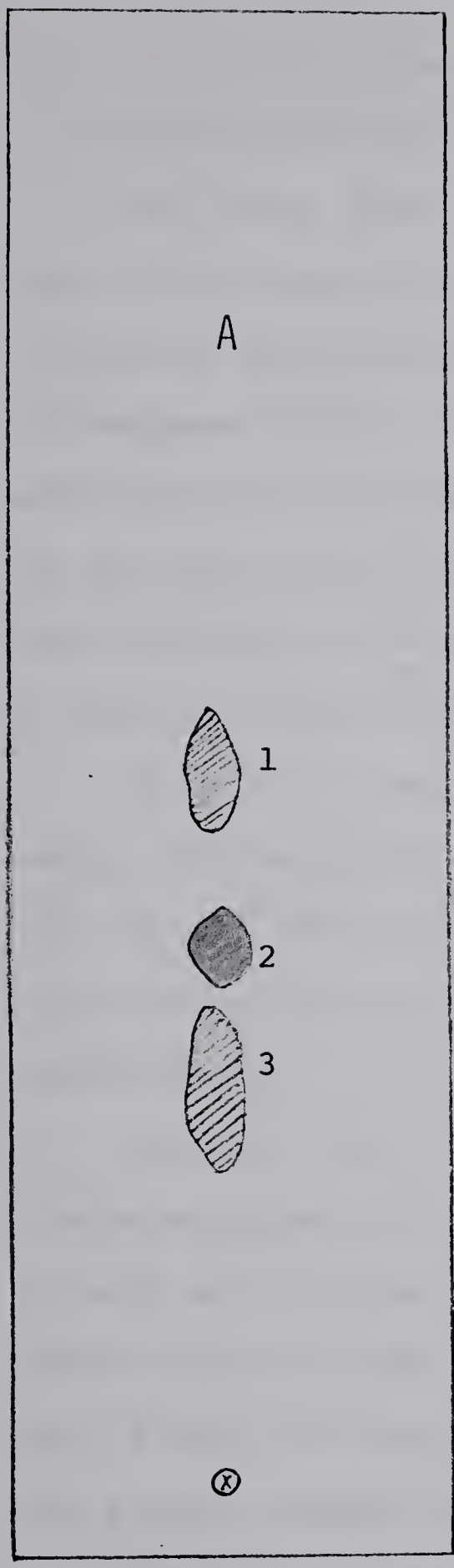
rarely causes any inconvenience.

In the preparation of 5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XV) (see Experimental section VII, 1 and VII, 5), 5,6-O-isopropylidene-3-O-(2'-methoxy-2'-propyl)-2-O-methyl-D-galactonolactone (XIX) was also observed by t.l.c. examination as a product when the reaction was allowed to continue for a longer period of time. Efforts to obtain the latter compound in high yield either by prolonged heating or using a higher excess of 2,2-dimethoxypropane were not successful. It appeared to lead only to more discoloration of the solutions (64). However, if dihydropyran or ethyl vinyl ether was added to the solution of 2-O-methyl-D-galactono-1,4-lactone (XIV) and 2,2-dimethoxypropane in 1,2-dimethoxyethane containing p-toluenesulfonic acid, which had been kept at room temperature for 2 h (see Experimental section VII, 3 and VII, 4) very high yields of either 5,6-O-isopropylidene-2-O-methyl-3-O-tetrahydropyranyl-D-galactonolactone (XVII) or 3-O-(1'-ethoxyethyl)-5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XVIII) were obtained.

When the tetrahydropyranyl ether (XVII) was reacted with excess methyl magnesium iodide, and the product was chromatographed on a column of silicic acid, both compound XX and the diastereoisomers of 1-deoxy-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-4-O-tetrahydropyranyl-D-galacto-heptitol (XXI) were isolated. Obviously, the THP group

was partially hydrolyzed in the course of chromatographic separation.

The reaction of 3-O-(1'-ethoxyethyl)-5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XVIII) with 20 equivalents of methyl magnesium iodide in anhydrous ether was as smooth as that of the THP ether (XVII). The solution was homogeneous and no precipitate was observed during the course of the reaction. The product consisted of three components as indicated by a thin-layer chromatogram which is illustrated in Fig. 16. The middle bluish spot, 2, was some undesired by-product; the other two spots, 1 and 3, were tentatively assigned as the diastereoisomers of 1-deoxy-4-O-(1'-ethoxyethyl)-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-D-galacto-heptitol (XXII). This was confirmed when the crude syrup, dissolved in aqueous acetic acid and freeze-dried under high vacuum, gave a compound which had the same Rf value as the authentic 1-deoxy-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-D-galacto-heptitol (XX) together with the fast moving bluish spot. Purification by chromatography afforded a material which had the n.m.r. spectrum identical to that of compound XX. The yield in the Grignard reaction was approximately 65% based on the isolation of compound XX after the crude product (XXII) had been passed through a column of silicic acid resulting in the complete removal of the ethoxyethyl group. This is



1 and 3 diastereoisomers of 1-deoxy-4-O-(1'-ethoxyethyl)-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-D-galacto-heptitol (XXII)

2. some undesired by-product (bluish color)

5 and 7 5-O-acetyl-1-deoxy-4-O-(1'-ethoxyethyl)-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-D-galacto-heptitol (XXIV)

6 some undesired by-product (bluish color)

4 1-deoxy-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-D-galacto-heptitol (XX)

Fig. 16. Chromatograms of compounds XX, XXII, and XXIV; A with ether as the developing solvent, B with 45% acetone, 55% toluene.

not surprising since 1-ethoxyethyl ethers are known to be more acid-labile than are tetrahydropyranyl ethers (73).

The yield (65%) was a gratifying improvement on that (36%) obtained when 3-O-acetyl-5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XVI) was used in place of compound XVIII. As mentioned before, some precipitate was observed during the course of the Grignard reaction on the acetylated γ-lactone derivative (XVI). Thus, the poor yield may be due to the low solubility in ether of a reaction intermediate.

The n.m.r. spectra of 5,6-O-isopropylidene-2-O-methyl-3-O-tetrahydropyranyl-D-galactonolactone (XVII) and 3-O-(1'-ethoxyethyl)-5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XVIII) are shown in Fig. 11 and 12, respectively.

The THP ether (XVII) is easily recognized as a diastereoisomeric pair by the presence of two methoxyl signals at τ6.35 and 6.37. Judging from the relative intensities of these two signals, the diastereoisomers were formed in a ratio of about 2:1. The signals for the geminal methyl protons are at τ8.60 and 8.63.

The n.m.r. spectrum for the product XVIII showed a singlet for the methoxyl group (τ6.33) and signals compatible with that expected for a single ethoxy group. Also, the product seemed homogeneous on examination by t.l.c., although in theory the syrup must be expected to consist of two diastereoisomers.

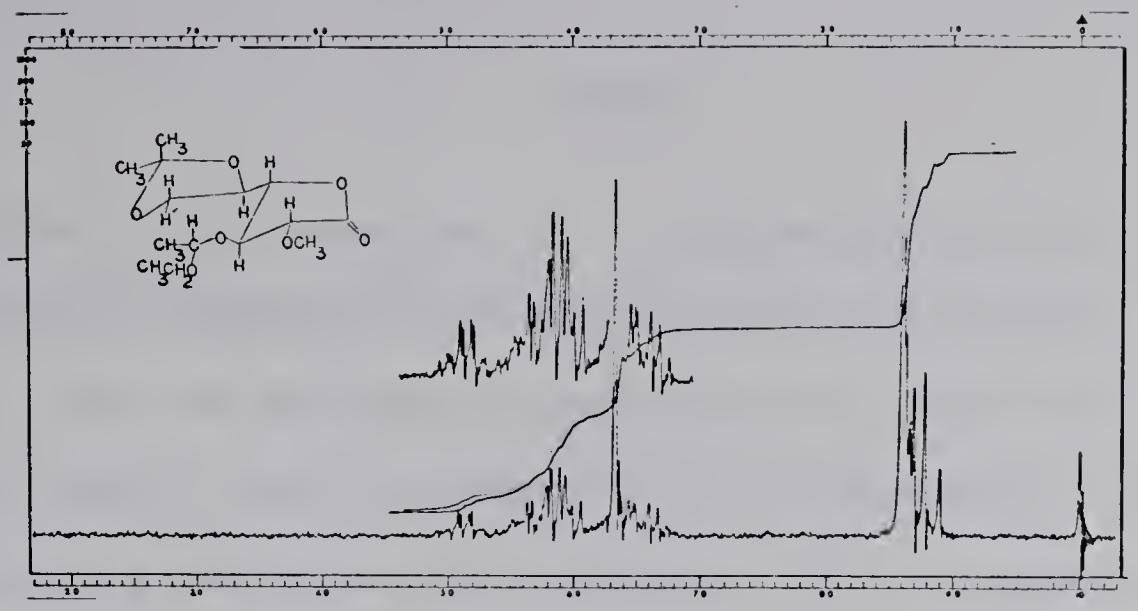


Fig. 12. N.m.r. spectrum (60 MHz) of 3-O-(1'-ethoxyethyl)-5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XVIII)($CDCl_3$).

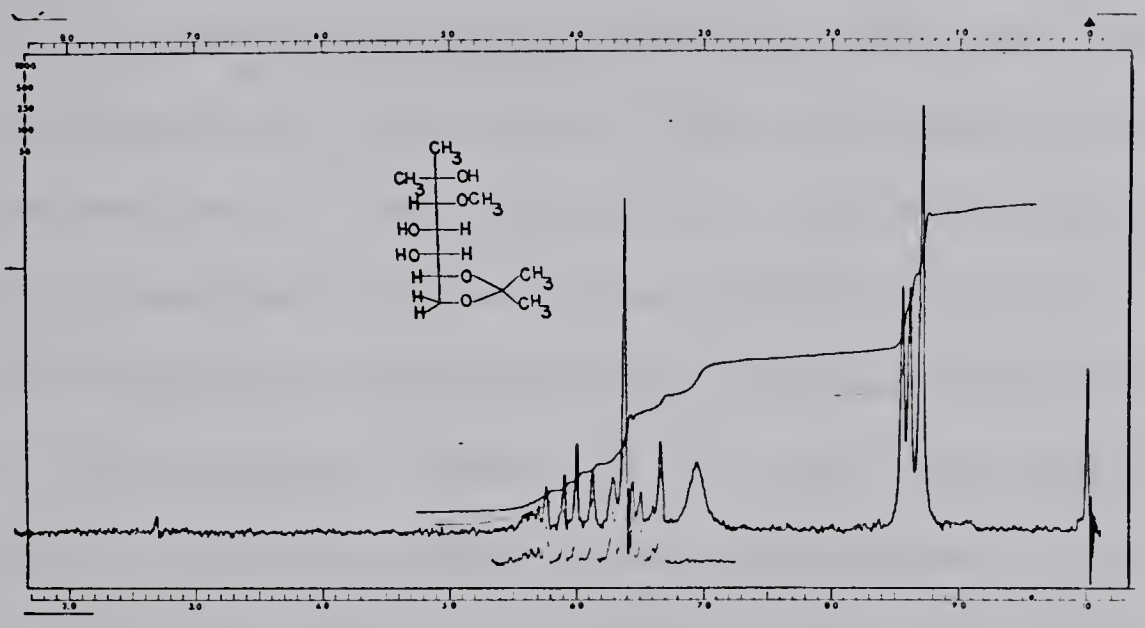


Fig. 13. N.m.r. spectrum (60 MHz) of 1-deoxy-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-D-galacto-heptitol(XX)($CDCl_3$).

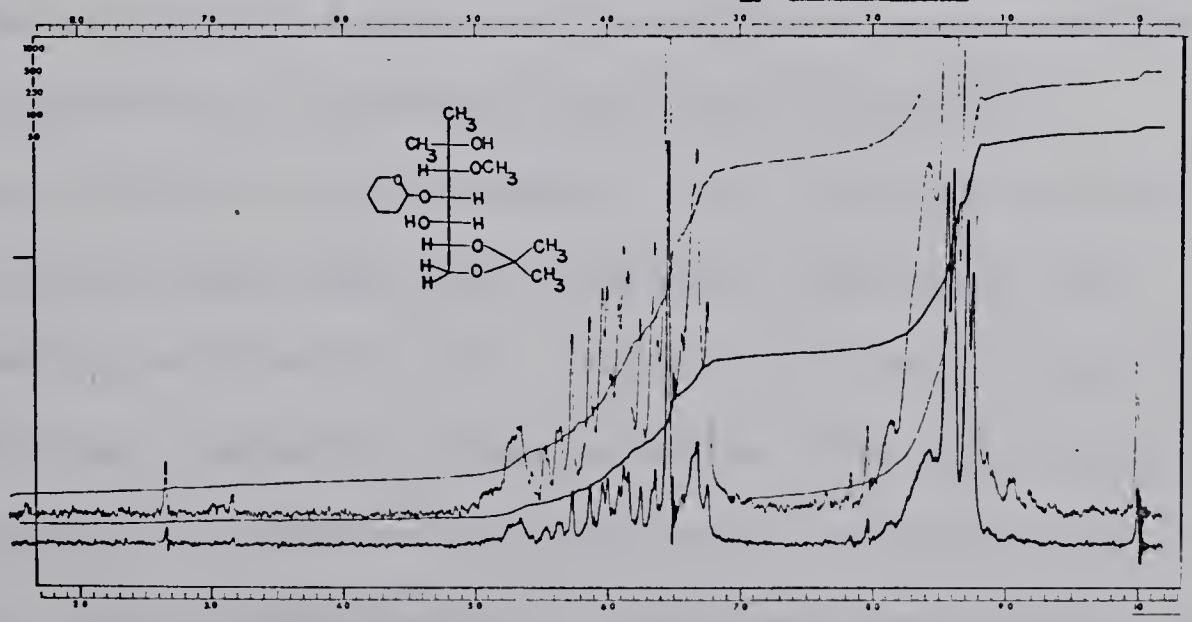


Fig. 14. N.m.r. spectrum (60 MHz) of 1-deoxy-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-4-O-tetrahydropyranyl-D-galacto-heptitol (XXI)($CDCl_3$).

In the n.m.r. spectrum of 5,6-O-isopropylidene-3-O-(2'-methoxy-2'-propyl)-2-O-methyl-D-galactonolactone (XIX) in $CDCl_3$, the two methoxyl signals were at τ6.22 and 6.52 with the former signal assigned to the 2-methoxyl protons. The C-methyl protons of the isopropylidene group absorbed at τ8.47, 8.53. The two geminal methyl protons appeared as a singlet at τ8.62.

The n.m.r. spectra of 1-deoxy-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-D-galacto-heptitol (XX) and its 4-O-tetrahydropyranyl derivative (XXI) are shown in Fig. 13 and 14 respectively. For compound XX, the broad signal at τ6.95 was assigned to the three hydroxyl protons since it disappeared when the $CDCl_3$ solution was shaken with D_2O. The methoxyl signal is at τ6.38, and the C-methyl signals of the isopropylidene group absorbed at τ8.57 and 8.63. The two C-methyl protons of the t-carbinol derivative appeared as a singlet at τ8.72.

When compound XX was acetylated with acetic anhydride in the presence of pyridine, the 4,5-di-O-acetyl derivative (XXIII) was obtained. The t-hydroxyl group was not acetylated under the condition employed (see Experimental section IX, 1). This is not surprising since t-alcohols are generally less reactive than sec-alcohols. The signals for the two acetoxy groups appeared at τ7.88 and 7.92. The broad signal at τ7.43 was assigned to the t-hydroxyl proton and confirmed by exchange with D_2O.

The signals at τ4.63-4.73 integrated for two protons and were assigned to H-4 and H-5 since the deshielding effect of the acetoxy groups requires these hydrogens to give signals in this region of the spectrum.

For the 4-O-tetrahydropyranyl derivative (XXI), the methoxyl signal is at τ6.46, and the C-methyl proton of the isopropylidene group absorbed at τ8.57 and 8.61. The signal centered at τ8.44 was assigned to the six methylene protons at positions 3,4,5 of the tetrahydropyranyl group. The signals for the two C-methyl protons were at τ8.72 and 8.76.

Since 1-deoxy-4-O-(1'-ethoxyethyl)-6,7-O-isopropylidene-2-C-methyl-3-C-methyl-D-galacto-heptitol (XXII) has not been obtained in a pure state, it would not be profitable to discuss its n.m.r. spectrum. When the crude compound XXII was acetylated with acetic anhydride in the presence of pyridine, the 5-O-acetyl derivative (XXIV) was obtained as indicated by the appearance of a signal for the acetoxy group at τ7.91 with an intensity equal to that of a methoxyl group. The appearance of the two methoxyl signals at τ6.55 and 6.58 showed that the product XXIV was a pair of diastereoisomers.

The final stage in the preparation of 2-O-acetyl-β-noviose (XXV) involved reaction of compound XXIV with a mole of periodic acid in aqueous acetic acid. It was expected that under these strongly acidic conditions

Table VIII

N.m.r. parameters (60 MHz, $CDCl_3$) of

compound XX and its derivatives

Compound	τ						
	OH	OCH_3	$O\diagup\!\diagdown^{CH_3}_{O\diagdown\!\diagup CH_3}$	$\times^{CH_3}_{CH_3}$	OAc	H-4 & H-5	$-(CH_2)_3-$
XX	6.95	6.38	8.57, 8.63	8.72	-	-	-
XXIII	7.43	6.42	8.58, 8.67	8.77, 8.81	7.88; 7.92	4.63-4.73	-
XXII	-	6.42	-	-	-	-	-
XXIV	-	6.55, 6.58	-	-	7.91	-	-
XXI	-	6.46	8.57, 8.61	8.72, 8.76	-	-	8.44
XXXVII in D_2O	-	6.61	8.54, 8.59	-	-	-	-

XX 1-deoxy-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-D-galacto-heptitol

XXIII 4,5-di-O-acetyl-1-deoxy-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-D-galacto-heptitol

XXII 1-deoxy-4-O-(1'-ethoxyethyl)-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-D-galacto-heptitol

XXIV 5-O-acetyl-1-deoxy-4-O-(1'-ethoxyethyl)-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-D-galacto-heptitol

XXI 1-deoxy-6,7-O-isopropylidene-2-C-methyl-3-O-methyl-4-O-tetrahydropyranyl-D-galacto-heptitol.

XXXVII sodium 5,6-O-isopropylidene-2-O-methyl-D-galactonate.

(<pH3), both the acetal and ketal groups would undergo hydrolysis readily and that the liberated tetraol with the vicinal glycol at the 6- and 7-positions would be cleaved to provide the 2-O-acetylnoviose and formaldehyde. In fact, the method provided crystalline 2-O-acetyl-β-noviose (XXV) upon isolation. Acetyl group migrations involving isomerization by intramolecular transesterification are well known to take place in alkaline medium (133). However, under the acidic conditions of the reaction, the sensitive group seems to be unaffected (112).

Best results were obtained when the periodic acid oxidation of compound XXIV was performed in the dark and at low temperature (7°). This is readily understandable since periodate solutions decompose at a measurable rate in sunlight and non-specific oxidation tends to occur at high temperature. The periodate and iodate ions were removed conveniently by passing the solution through a column of Amberlite IRA-400 (acetate form) (77). Crystalline 2-O-acetyl-β-noviose (XXV) was isolated as the final product in 43% yield from 3-O-(1'-ethoxyethyl)-5,6-O-isopropylidene-2-O-methyl-D-galactonolactone (XVIII). The overall yield of compound XXV from the readily accessible 1,6-anhydro-3,4-O-isopropylidene-β-D-galactose (XI) in seven stages was 35%, when the intermediates were not purified. This is undoubtedly a vast improvement over the synthesis of noviose from D-glucose (20) in fifteen steps which had the overall yield of less than 4%.

The n.m.r. spectrum of crystalline 2-O-acetyl-β-noviose (XXV) is shown in Fig. 17. When DMSO-d_6 was used as solvent, the couplings of the hydroxyl protons with geminal hydrogens could be readily observed. The quartet at τ5.17 was assigned to H-1, and since exchange of the hydroxyls with D_2O caused a change of the signal to that of a doublet with a spacing of 1.5 Hz, the larger spacing (8.0 Hz) in the quartet must have arisen through coupling of H-1 with the O-H_1. The septet at τ6.30 was assigned to H-3 for similar reasons. Thus, the exchange led to a quartet through the disappearance of coupling (6.5 Hz) with O-H_3. The residual quartet had spacings of 3.0 and 10 Hz assigned to $J_{2,3}$ and $J_{3,4}$, respectively. The signal for H-4 is the sharp doublet with a spacing of 10 Hz at τ7.10. The two doublets at τ3.84, 5.06 were assigned to O-H_1 and O-H_3, respectively. This was verified when the solution was shaken with D_2O resulting in the disappearance of these two signals. The exchange also led to recognition of the signal for H-2 (τ5.0) which partly coincided with the signal for O-H_3. In view of the magnitude of $J_{3,4}$, compound XXV must exist in the 1C chair conformation shown. Also, the n.m.r. spectrum requires that the acetyl group be at the 2-position and the large value for $J_{H_1\text{-}OH_1}$ was clearly suggestive of an equatorial hydroxyl group (134). This would require the β-L-configuration for the crystalline 2-O-acetylnoviose.

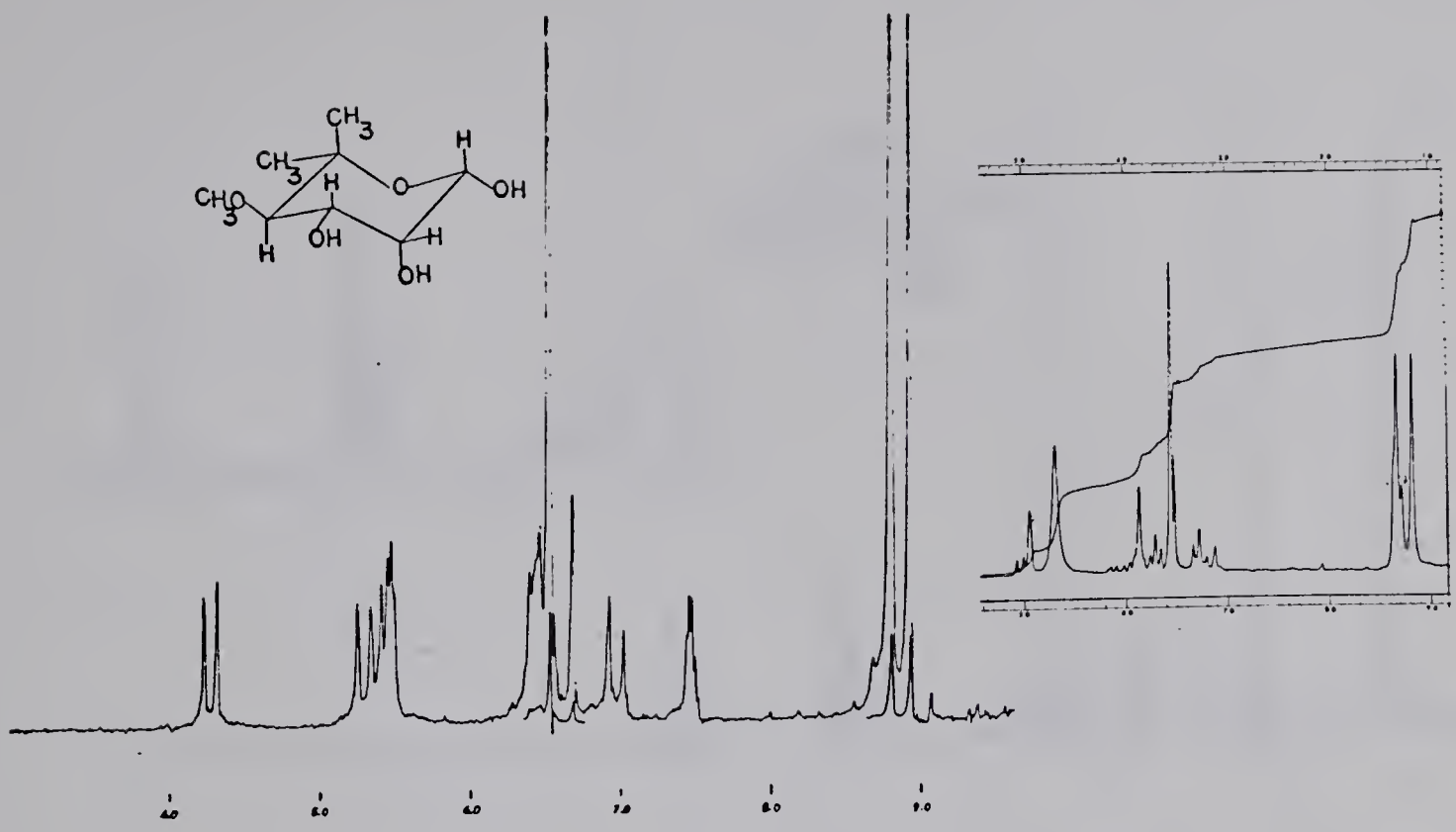


Fig. 15. N.m.r. spectrum (100 MHz) of β-noviose (IV) (DMSO-d_6). Inset (60 MHz) (D_2O).

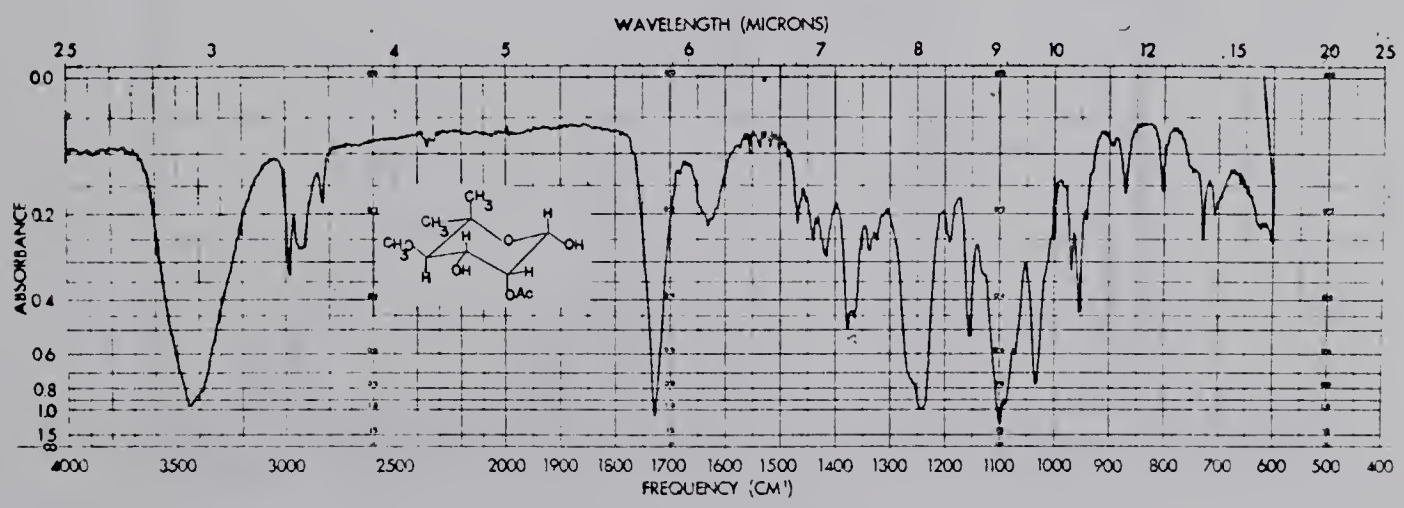


Fig. 18. Infrared spectrum of 2-O-acetyl-β-noviose (XXV) (potassium bromide pellet).

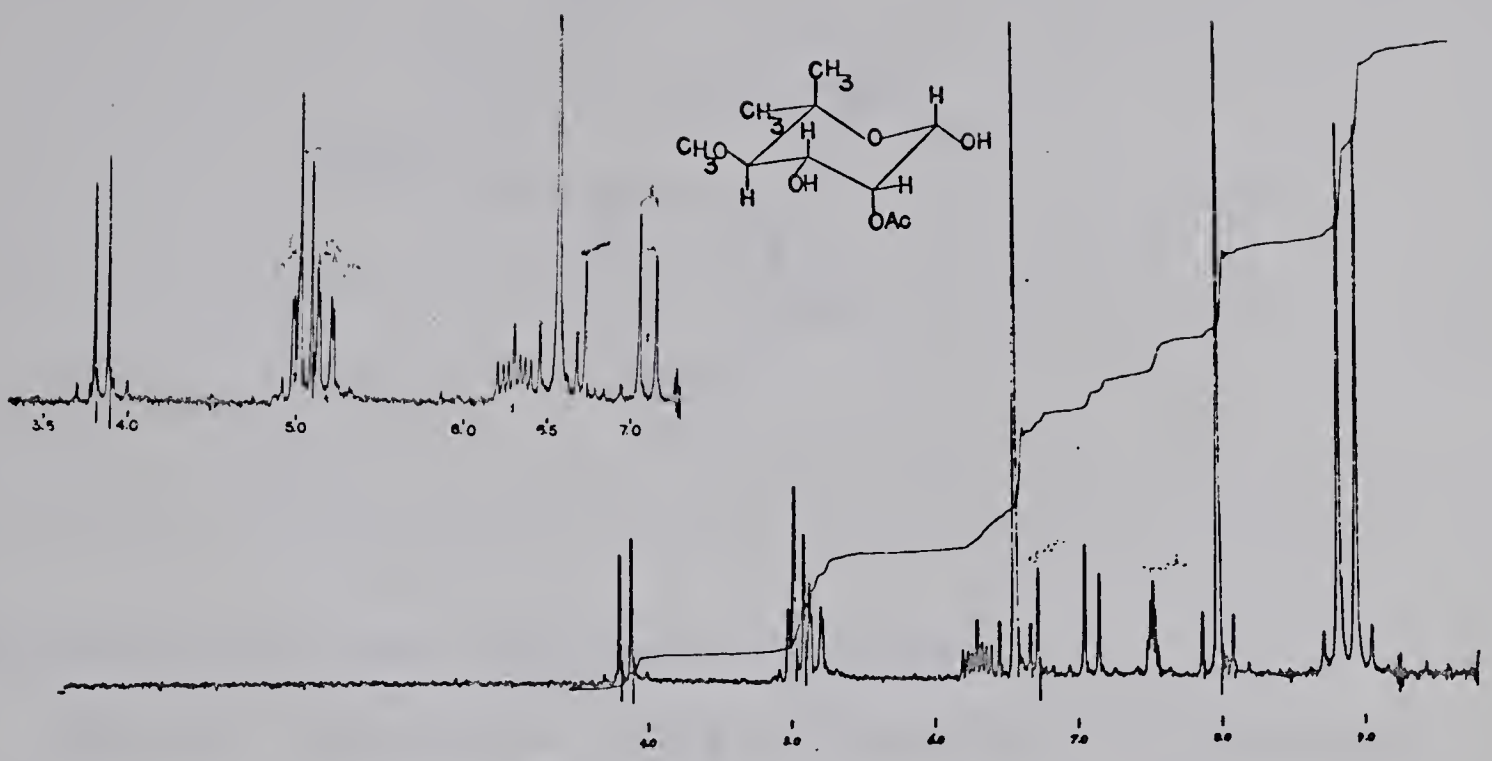


Fig. 17. N.m.r. spectrum (100 MHz) of 2-O-acetyl-β-noviose (XXV) (DMSO-d_6).

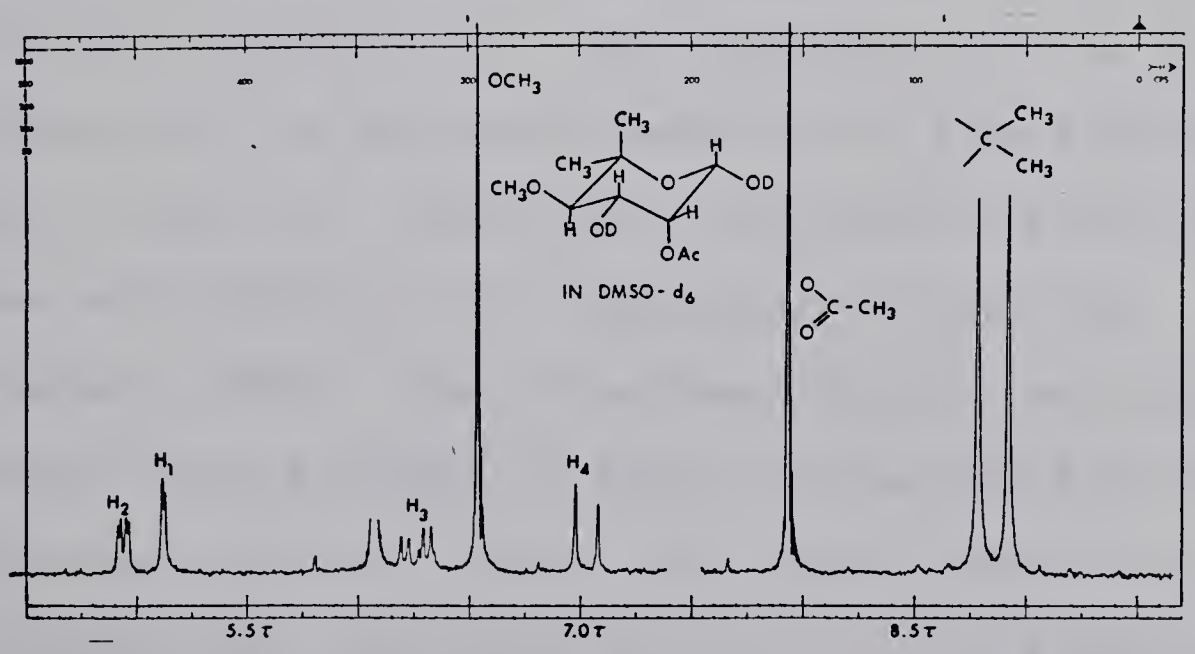
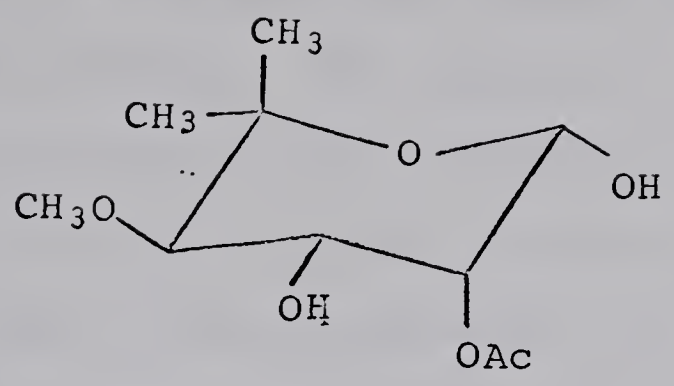


Fig. 17. N.m.r. spectrum (100 MHz) of the O-deuterated 2-O-acetyl-β-noviose (XXV) (DMSO-d_6).





XXV

This conclusion was confirmed as follows.

When the crystalline 2-O-acetylnoviose was acetylated at low temperature with acetic anhydride and pyridine, β-noviose triacetate (XXVI) was obtained. However, acetylation in the presence of zinc chloride at 50° gave the α-anomer predominantly. The assignment of the α- and β-configuration for noviose triacetate will be discussed in detail later on. Furthermore, crystalline β-noviose (IV) was acetylated at low temperature to give the β-triacetate (XXVI). The β-configuration of the crystalline noviose has been assigned by Angyal on the basis of its mutarotation and n.m.r. (44). The optical rotation of 2-O-acetylnoviose, which had $[\alpha]_D$ +60° in 98% ethanol and decreased to +26° after 50 h at room temperature, appeared to support the assignment of the β-L-configuration for this compound.

When D_2O was used as solvent for the n.m.r. spectrum

of 2-O-acetyl-β-noviose (XXV), the anomerization and acetyl migration could be observed as indicated by the presence of five acetoxy signals. The signal at τ7.72 was assigned to the acetoxy protons of the β-anomer of the 2-acetate (XXV) since it had the strongest intensity. When the solution was kept at room temperature for 17 h, the intensity of the signals at τ7.72, 7.74 was far greater than the signals at τ7.73, 7.75 and 7.76. The signal at τ7.74 probably belonged to the acetoxy protons of the α-anomer of 2-O-acetylnoviose. The exact ratios could not be calculated. The doublet with a large spacing (10 Hz) at τ6.67 was assigned to H-4 for 2-O-acetyl-β-noviose (XXV). The magnitude of $J_{3,4}$ indicates that 2-O-acetyl-β-noviose (XXV) also exists in the 1C chair conformation in D_2O.

The infrared spectrum of crystalline 2-O-acetyl-β-noviose (XXV) is shown in Fig. 18. The carbonyl absorption of the acetyl group was at 1730 cm^{-1}. The hydroxyl absorption was at 3450 cm^{-1}. The twin infrared bands at 1365 and 1379 cm^{-1} indicated the presence of gem-dimethyl groups.

Deacetylation of 2-O-acetyl-β-noviose (XXV) with triethylamine in aqueous methanol gave crystalline β-noviose which was identical to authentic β-noviose obtained from methyl α-novioside 3-(2-pyrrolecarboxylate). The n.m.r. spectrum of β-noviose in D_2O has been published (44) and the parameters are reproduced in

Table IX

N.m.r. parameters (100 MHz, DMSO-d_6) of 2-O-acetylnoviose and noviose

Compound	O-H_1	$J_{OH_1-H_1}$	O-H_2	$J_{OH_2-H_2}$	OH_3	$J_{OH_3-H_3}$	H-1	$J_{1,2}$	H-2	$J_{2,3}$	H-3	$J_{3,4}$	H-4
	(τ)	(Hz)	(τ)	(Hz)	(τ)	(Hz)	(τ)	(Hz)	(τ)	(Hz)	(τ)	(Hz)	(τ)
XXV	3.84	8.0	-	-	5.06	6.5	5.17	1.5	5.0	3.0	6.30	10	7.10
"(D_2O added)	-	-	-	-	-	-	4.79	1.5	4.64	3.5	5.94	10	6.67
IV	4.28	9.0	5.46	3.0	5.46	8.0	5.30	-	~6.40	-	6.50	10	6.98
IVα	3.97	4.5	-	-	-	-	-	-	-	-	-	8.5	6.93

Compound	τ		
	OCH_3	OAc	CH_3, CH_3
XXV	6.54	7.96	8.80, 8.92
XXV (D_2O added)	6.36	7.72	8.58, 8.74
XXVα (D_2O added)	6.41	7.74	-
IV	6.55	-	8.83, 8.96
IVα	6.58	-	-

XXV 3-O-acetyl-β-noviose
XXVα 2-O-acetyl-α-noviose
IV β-noviose
IVα α-noviose

Table II. Its spectrum in DMSO-d_6 is shown in Fig. 15. The doublet with a large spacing (9.0 Hz) at τ4.28 was assigned to O-H_1. Irradiation at this resonance frequency collapsed the doublet at τ5.30 to a singlet. Therefore, the signal for H-1 must be at this position since the signals for H-2 and H-3 are expected to be complex. It follows that the value of $J_{1,2}$ is very small. The signal for H-4 is the sharp doublet with a spacing of 10 Hz at τ6.98. Irradiation at this resonance frequency changed the appearance of the signals at τ6.50. The signal for H-3 must therefore be at this position. The chemical shifts of O-H_2 and O-H_3 were nearly the same (τ5.46). Irradiation at the resonance frequency of H-3 (τ6.50) collapsed the signals centered at τ5.46 to a doublet with a spacing of 3.0 Hz. Therefore, the spacing (8.0 Hz) must have arisen through coupling of H-3 and the O-H_3. The smaller spacing (3.0 Hz) was that of $J_{OH_2-H_2}$. The equatorial hydroxyls were found to have larger coupling constants than their axial counterparts. This is in agreement with the observations by Casu and co-workers (134). When β-noviose was allowed to anomerize, the signal for the O-H_1 of the α-anomer was observed at τ3.97 ($J^{\alpha}_{OH_1-H_1}$ ≃4.5 Hz). The signal for H^{α}-4 is the doublet with a spacing of 8.5 Hz at τ6.93. The decrease of the spacing from 10 to 8.5 Hz for the coupling of H-3 with H-4 for the α- and β-noviose, respectively is parallel

to that of crystalline noviose in D_2O in which $J^{\beta}_{3,4}$ ≃9.5 Hz and $J^{\alpha}_{3,4}$ ≃7.7 Hz. The detailed explanation has been given by Angyal (44).

As mentioned previously, the acetylation of either 2-O-acetyl-β-noviose (XXV) or β-noviose (IV) at low temperature with acetic anhydride and pyridine gave the same syrupy β-noviose triacetate (XXVI), whereas the acetylation of compound XXV in the presence of zinc chloride at 50° gave the α-anomer predominantly. The n.m.r. spectra of β- and α-noviose triacetate are shown in Fig. 19 and 20, respectively.

For the low temperature acetylated product, the quartet at τ4.57 was assigned to H-2 with $J_{1,2}$ ≃1.5 Hz and $J_{2,3}$ ≃3.5 Hz. Another quartet at τ4.89 was assigned to H-3 with the larger spacing (10 Hz) arising through coupling of H-3 with H-4. The signal for the anomeric proton is at the lowest field (τ4.02). The doublet at τ6.65 is the signal for H-4. For the high temperature acetylated product, the signal at τ4.62 was assigned to H^{α}-3. The signal for H^{α}-4 is the sharp doublet with a spacing of 9.5 Hz at τ6.62. The quartet at τ4.78 was assigned to H^{α}-2 with $J^{\alpha}_{1,2}$ ≃2.0 Hz and $J^{\alpha}_{2,3}$ ≃3.5 Hz. The fact that H^{α}-3 (τ4.62) absorbed at a lower field than H-3 (τ4.89) of the low temperature acetylated product, is a convincing proof that the noviose triacetate obtained by the low temperature procedure has the β-configuration. For the α-anomer,

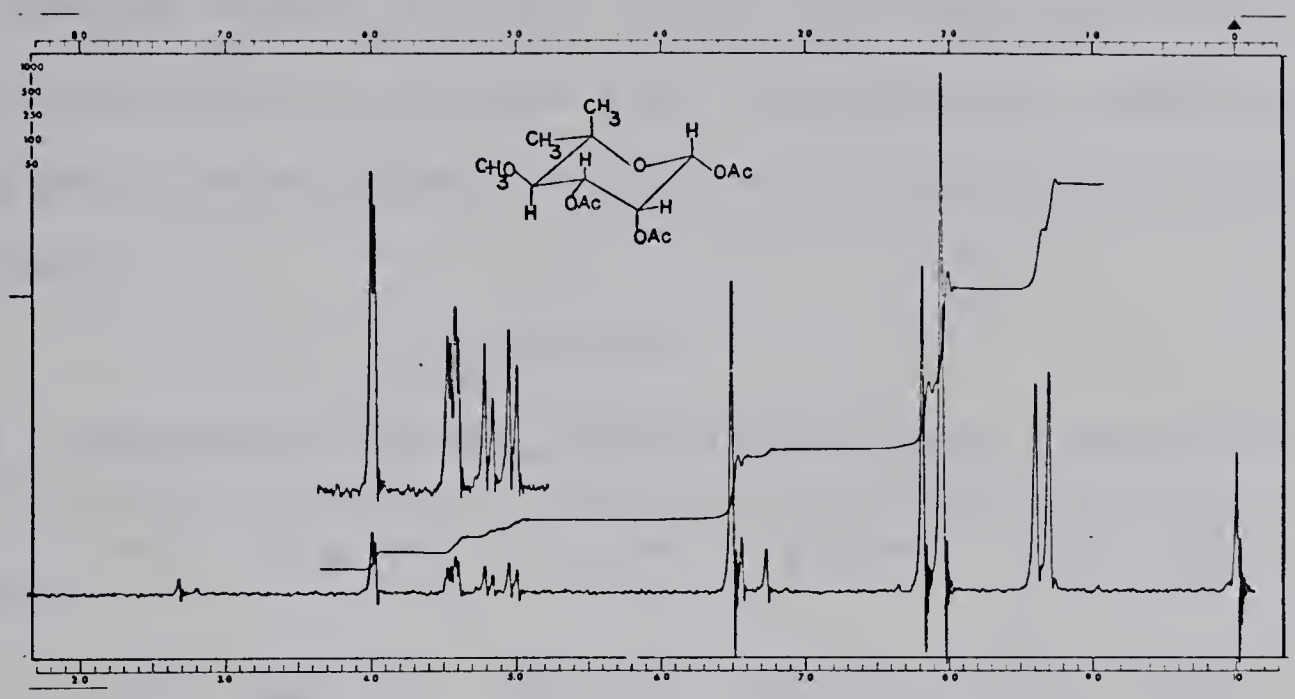


Fig. 19. N.m.r. spectrum (60 MHz) of β-noviose triacetate (XXVI) ($CDCl_3$).

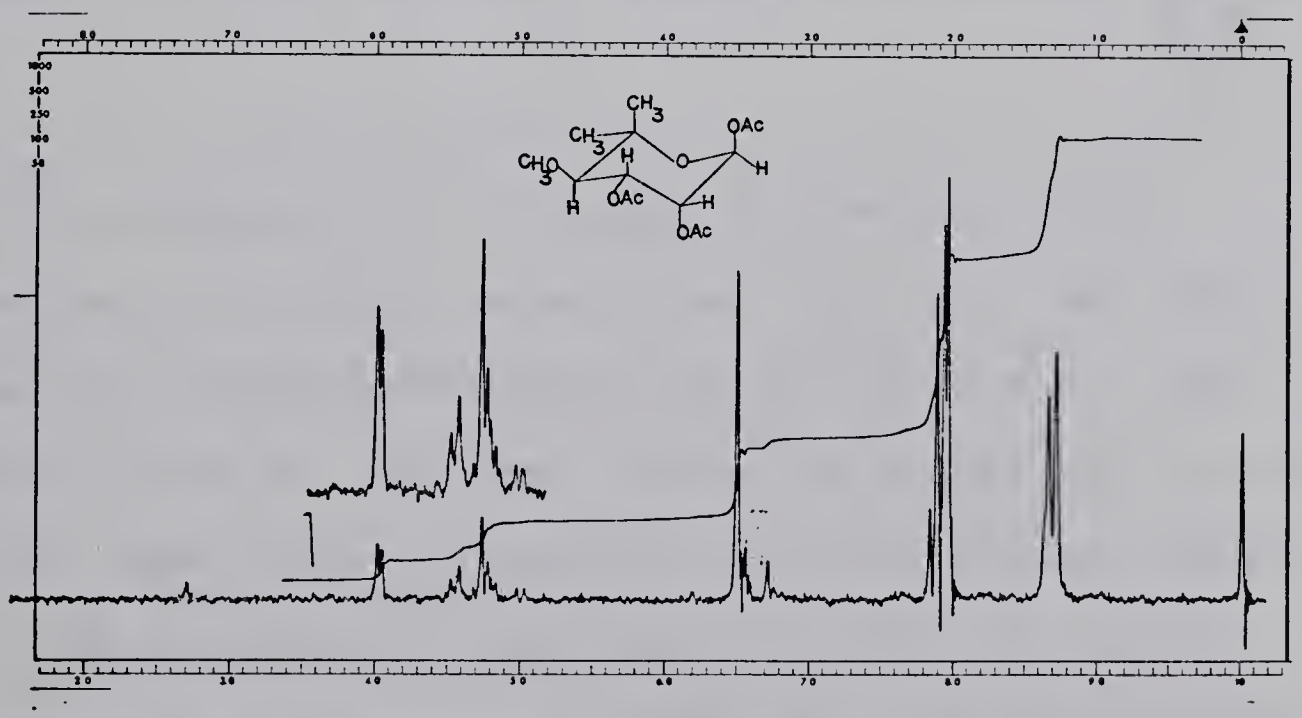
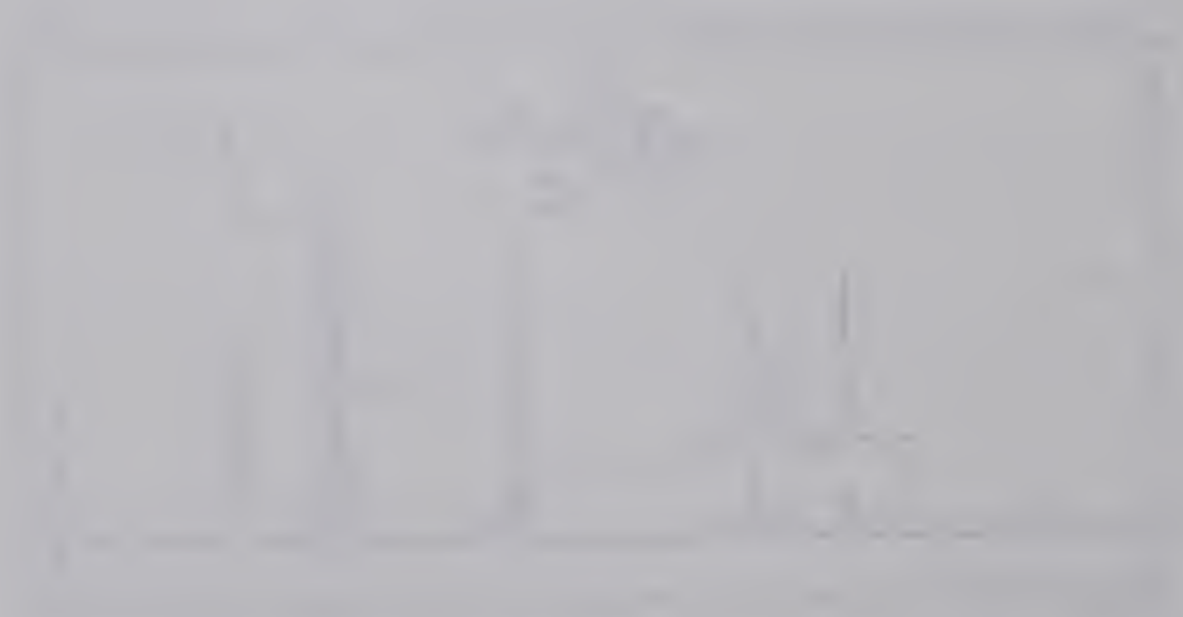


Fig. 20. N.m.r. spectrum (60 MHz) of α-noviose triacetate (XXVIα) with a small amount of the β-isomer (XXVI)($CDCl_3$).





H^{α}-3 was deshielded by the opposing axial acetoxy group at C-1, and as a result, it absorbed at a lower field than the observed signal for H^{β}-3 (113). The optical rotation of compound XXVI, which had +50° in chloroform, appeared to support the assignment of the β-configuration to this compound.

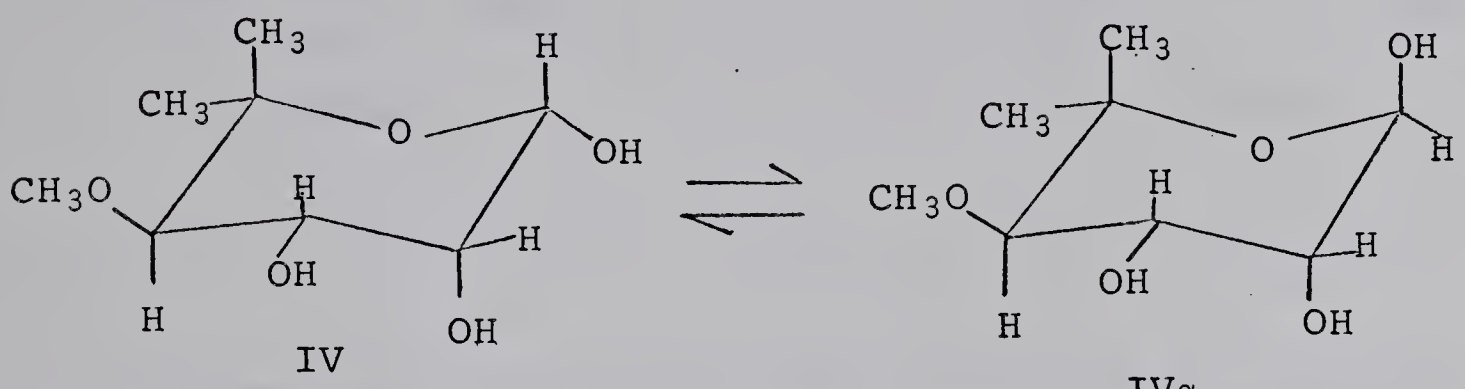
Table X

N.m.r. parameters (60 MHz, $CDCl_3$) of noviose triacetate

Compound	H-1 (τ)	$J_{1,2}$ (Hz)	H-2 (τ)	$J_{2,3}$ (Hz)	H-3 (τ)	$J_{3,4}$ (Hz)	H-4 (τ)	O-CH_3 (τ)	-OAc (τ)	CH_3 / CH_3 (τ)
β-anomer	4.02	1.5	4.57	3.5	4.89	10	6.65	6.49	7.82, 7.95	8.60, 8.71
α-anomer	4.01	2.0	4.78	3.5	4.62	9.5	6.62	6.49	7.88, 7.93, 7.97	8.65, 8.72

The production of α-noviose triacetate (XXVIα) predominantly at high temperatures indicates that this product is the thermodynamically more stable one. This contrasts with the novioses studied by Angyal and co-workers (44) who found that, in aqueous solution, noviose exists as α- and β-anomers in the ratio of 26:74 (±2) which corresponds to a free-energy difference of 0.6 (±0.05) KCal/mole. They suggested that α-noviose exists as a conformational mixture with 30% of the C1 conformation. The presence of the C1 conformation (30%) in equilibrium decreases the free-energy of α-noviose by 0.2 Kcal/mole

owing to the entropy of mixing (44). The C1 conformation of β-noviose, being of much higher free-energy, makes a negligible contribution to the equilibrium free-energy.



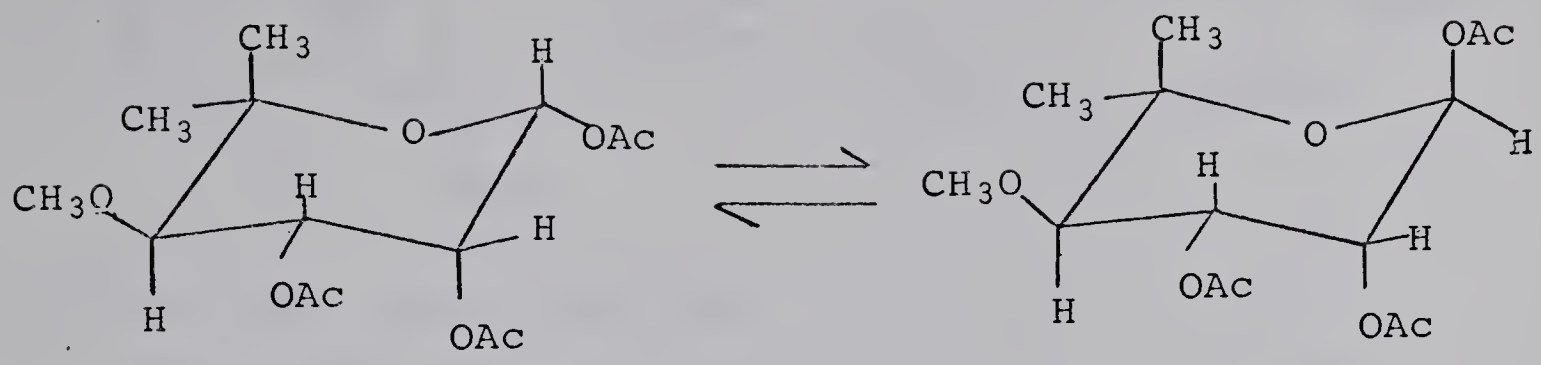
IV

IVα

$CH_3||H + O|O + A + \Delta 2$

$CH_3||O + O||H$ — entropy of mixing

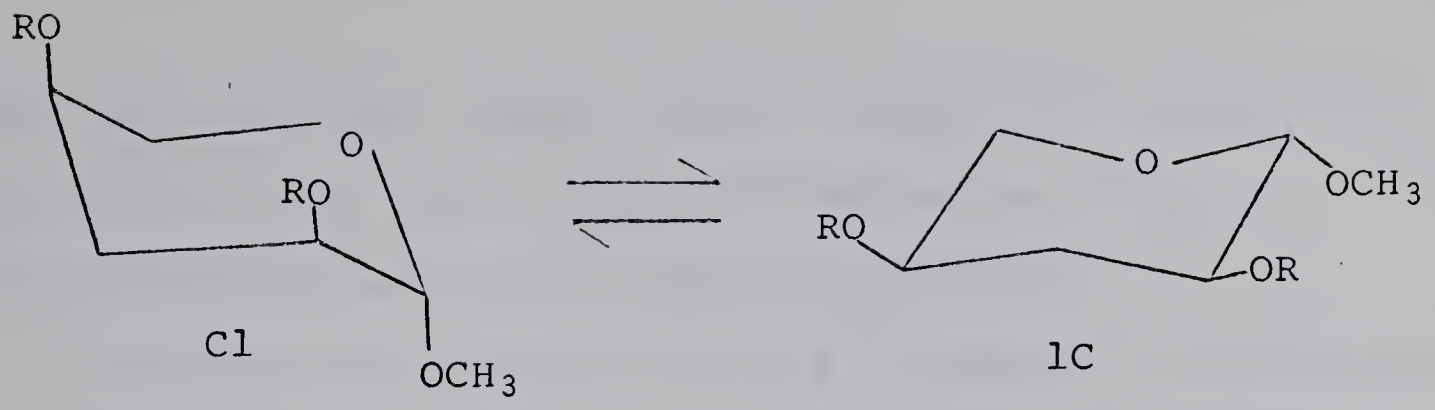
The following notation is used (128) in the subsequent equations: the interaction between two atoms in gauche relationship is represented by one oblique stroke, and that between two opposing axial substituents by two oblique strokes. Neglecting the common interactions, β-noviose (IV) has the following interactions $CH_3||H + O|O + A + \Delta 2$; and α-noviose (IVα) has the interactions $CH_3||O + O||H$ - entropy of mixing. Hence, $\Delta G° = 0.6 = CH_3||O + 0.45 - 0.2 - 0.9 - 0.35 - 1.0$, and $CH_3||O = 2.6$ Kcal/mole.



XXVI XXVIα

In contrast to noviose which exists to an extent of only 26% as the α-form at equilibrium in aqueous solution, the noviose triacetates when equilibrated in acetic anhydride-acetic acid containing zinc chloride, favored the α-form to an extent of greater than 80%. These results are in agreement with the observations that a hydrated hydroxyl group prefers the equatorial orientation to a greater extent than an acylated hydroxyl group (46, 144). Thus, for example, in unpublished work from this laboratory, Lemieux and Pavia have found that although a number of acyl derivatives of methyl 3-deoxy-β-L-*erythro*-pentopyranoside exist almost entirely in the C1 conformation shown, in all solvents including water, the deacylated glycoside in water prefers the 1C conformation.

Lemieux and Chü (145) have observed that equilibration of the configurationally related O-acetylated-D-lyxopyranose and D-mannopyranose provided the α-anomers in 92-95% yield.



R = Ac, Bz, Ms and p-NO_2-Bz

On this basis, the presence of an axial methyl group at C-5 of the noviose triacetates, which must lead to an interaction between the opposing axial acetoxy and methyl groups across an oxygen-containing bridge, has a rather surprisingly small effect on the relative stabilities of the two anomers. Indeed, on this basis, it may be concluded that the opposition of these two axial substituents leads to only very slight destabilization. A point of considerable interest is the fact that the anomeric effect must be a main driving force for the stabilization of the α-form (XXVIα) in spite of the absence of a proton at C-5. The nature of the anomeric effect is still not understood and this observation seems to eliminate the possibility that it arises from an electrostatic attraction between the substituent at the anomeric center and an electron-deficient hydrogen at C-5 in the pyranose form of unbranched sugars. This possibility deserved consideration since Martin, Hayami and Lemieux (146)

have observed that, under certain conditions, halide ions can complex with the C-1 and C-5 hydrogens of the acetylated derivatives of β-D-glucopyranose.

In order to prepare β-noviose 1,2-(methyl orthoacetate) (XXIX) (Fig. 38) as an intermediate in the syntheses of a variety of aryl 3-O-acyl-α-noviosides, a 2,3-di-O-acetylnoviosyl halide is required. Attempts to prepare 2,3-di-O-acetylnoviosyl bromide were not successful; this may be due to the extreme lability of this compound.

Fully acetylated aldopyranoses of 1,2-trans configuration are known to react with aluminum chloride in cold chloroform to give poly-O-acetylglycosyl chlorides of 1,2-trans configuration (78). The fully acetylated aldopyranoses with a 1,2-cis configuration were found to be unreactive towards this reagent. The reaction probably belongs to the class of reaction in which displacement of a group at C-1 depends on participation by the neighbouring 2-acetoxy group (96).

When β-noviose triacetate (XXVI) was reacted with aluminum chloride in cold chloroform, a syrupy product, which consisted of three components as indicated by t.l.c., was obtained. The product gave a positive test for chloride and afforded 3-O-acetyl-β-noviose 1,2-(methyl orthoacetate) (XXVIII) when it was reacted with methanol in the presence of 2,6-lutidine and tetraethylammonium chloride. The fact that the anomeric 2,3-di-O-acetylnoviosyl

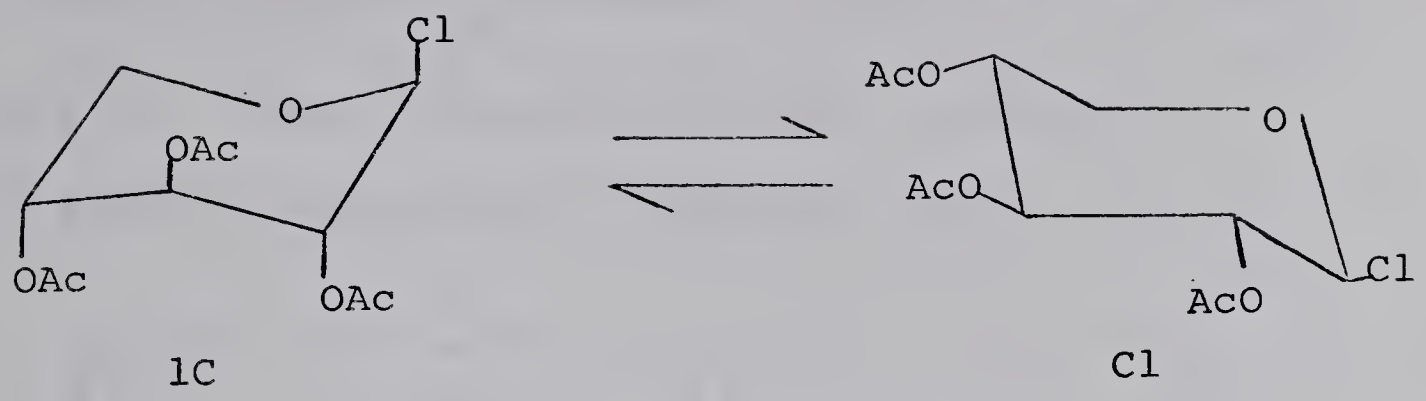
chlorides (XXVII) were formed from compound XXVI should not be too surprising. Lemieux and Brice (148) have reported that 1,2-trans-α-D-mannopyranose pentaacetate underwent exchange of acetate seven times more rapidly than the β-1,2-cis-anomer but eight times less rapidly than 1,2-trans-β-D-glucopyranose pentaacetate. The latter compound was 450 times more reactive than the α-1,2-cis-anomer. The anomeric effect, as expected, also plays quite an important role in the relative reactivity of the fully acetylated aldopyranoses. Thus, β-noviose triacetate (XXVI) probably reacts with aluminum chloride in cold chloroform seven times less rapidly than the α-anomer (XXVIα) which has the participation by the neighbouring 2-acetoxy group. However, this factor is not so serious as to render β-noviose triacetate (XXVI) unreactive towards this reagent, as generally observed for the fully acetylated aldopyranoses with a 1,2-cis configuration (78).

The n.m.r. spectrum of the crude 2,3-di-O-acetylnoviosyl chlorides (XXVII) is shown in Fig. 21 which indicated that the α-anomer was formed to the extent of 85%. This was calculated on the assumption that anomeric protons have different chemical shifts and the equatorial proton absorbs at a lower field than its axial counterpart (45). Two of the spots revealed on the chromatogram must be the anomers of 2,3-di-O-acetylnoviosyl

chloride, the other spot was not the starting material and was not characterized. Although chlorides of 1,2-*trans* configuration are normally stable in perfectly dry, non-polar solvents (78), this is not the case in the presence of even traces of water. Probably for this reason, it was not possible to separate the 2,3-di-*O*-acetylnoviosyl chlorides (XXVII) by chromatography.

The high yield of the α-chloride (XXVII) (~85%) is consistent with the high yield of the α-acetate (XXVIα) (>80%) which was obtained on equilibration of the noviose triacetates. Again, the interaction between the axial C5-methyl group and the axial C1-chlorine atom in the α-anomer (XXVII) appears anomalously small. This result has an important bearing on the work of Horton and co-workers (135) who have found that 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl chloride favors the 1C conformation shown, in chloroform, benzene or acetone. Hall and co-workers (136) have also found similar results for the corresponding fluoride. If the 1,3-diaxial non-bonded interactions were more serious than the *gauche* interactions plus the anomeric effect, the C1 conformation shown would be favored.

Lemieux and Hayami (80) investigated the anomerization of tetra-*O*-acetyl-D-glucopyranosyl chlorides and found that these reactions are strongly catalyzed by chloride ion. For this reason, tetraethylammonium chloride was added in the preparation of 3-*O*-acetyl-β-noviose 1,2-(methyl orthoacetate)(XXVIII) from



1C Cl

2,3-di-O-acetylnoviosyl chlorides (XXVII) with methanol in the presence of 2,6-lutidine. The n.m.r. spectrum of 3-O-acetyl-β-noviose 1,2-(methyl orthoacetate) (XXVIII) is shown in Fig. 22.

Only one diastereoisomer of 3-O-acetyl-β-noviose 1,2-(methyl orthoacetate) (XXVIII) was obtained as indicated by the n.m.r. spectrum. The chemical shifts of the methoxyl and the C-methyl of the orthoester group are at τ6.75 and 8.30, respectively. The quartet at τ5.40 was assigned to H-2 with $J_{1,2}$ = 2.5 Hz and $J_{2,3}$ = 4.0 Hz. The signal for the anomeric proton is at the lowest field

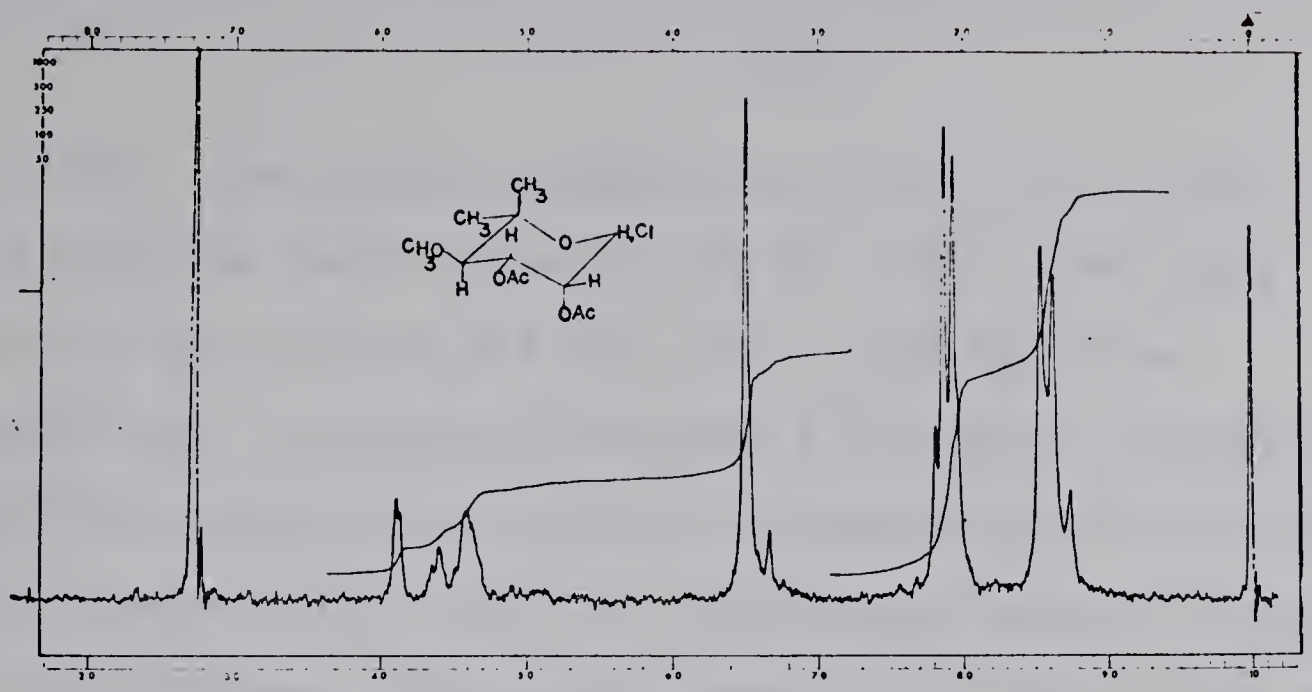


Fig. 21. N.m.r. spectrum (60 MHz) of mixture of 2,3-di-O-acetylnoviosyl chlorides (XXVII) ($CDCl_3$).

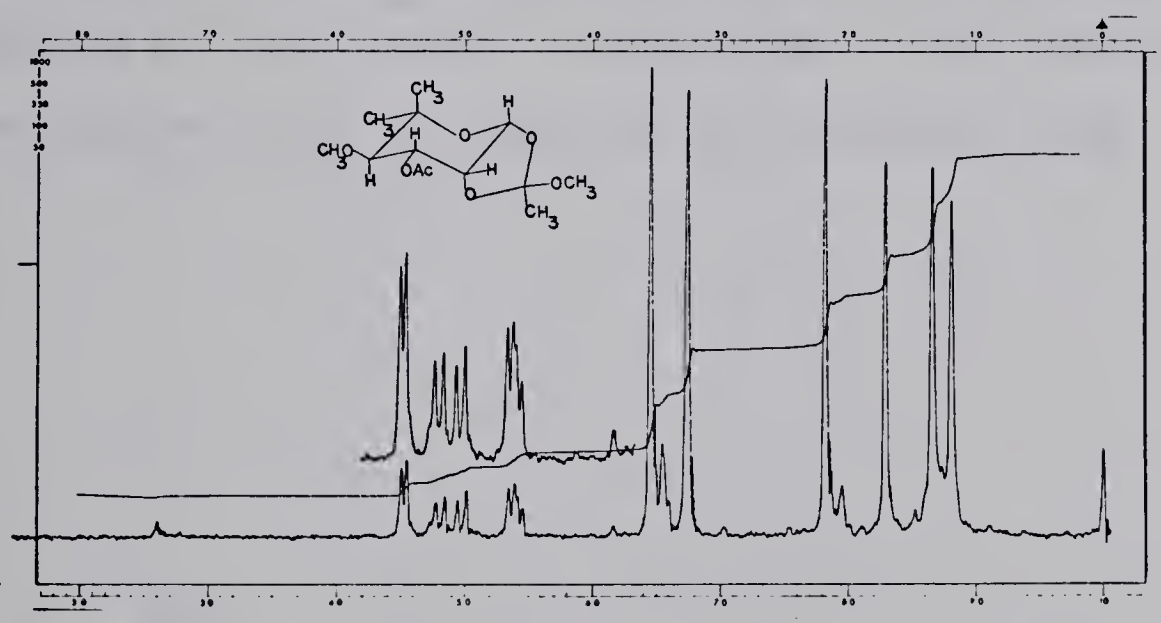


Fig. 22. N.m.r. spectrum (60 MHz) of 3-O-acetyl-β-noviose 1,2-(methyl orthoacetate) (XXVIII) ($CDCl_3$).

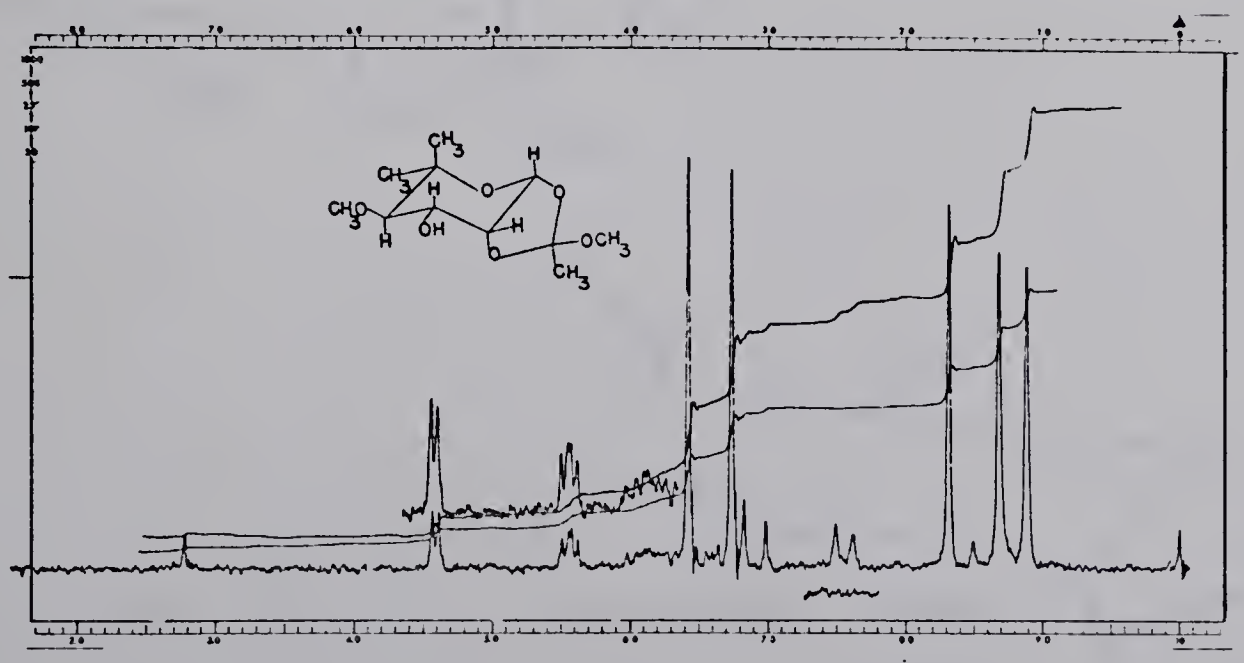
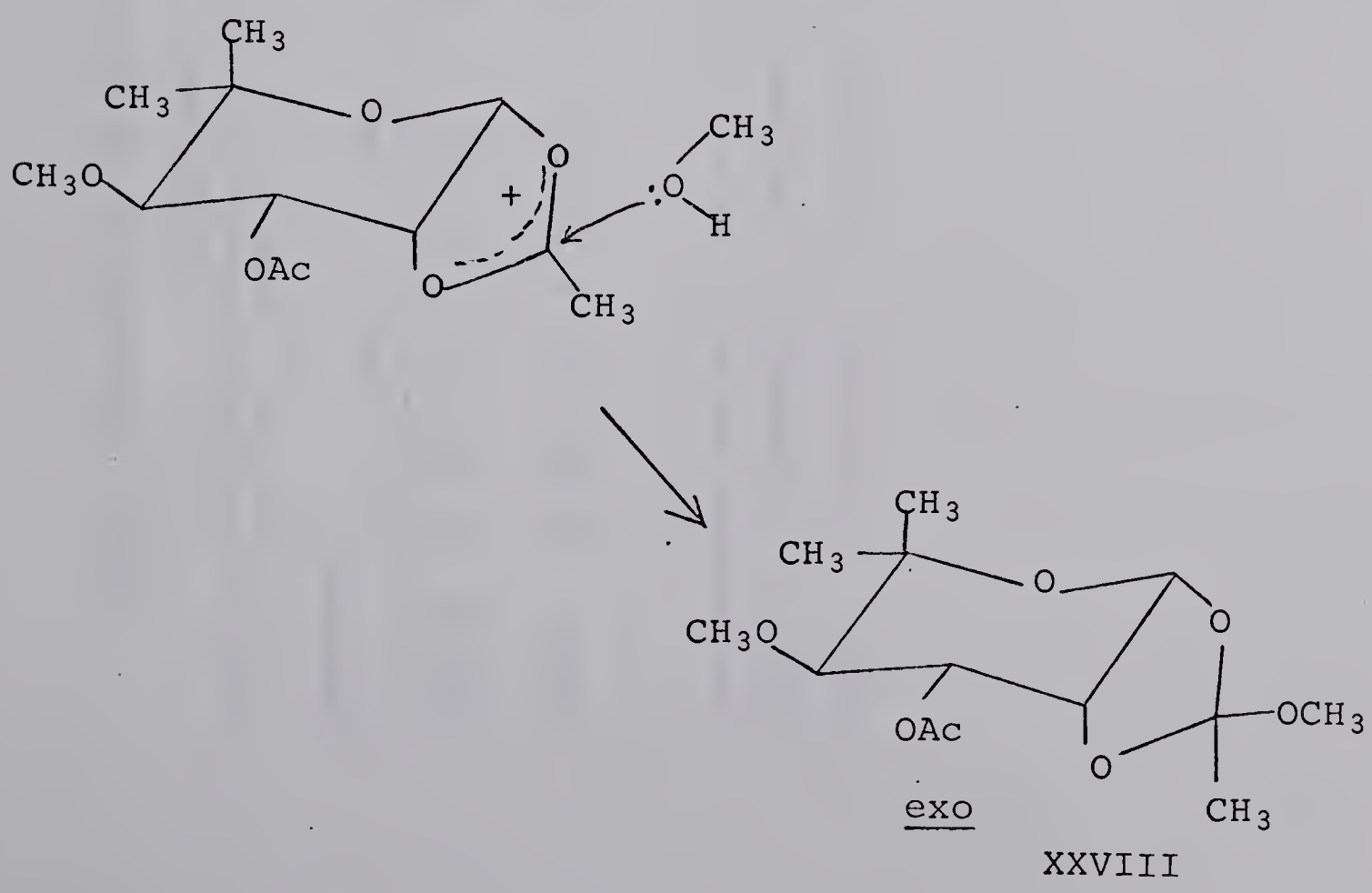


Fig. 23. N.m.r. spectrum (60 MHz) of β-noviose 1,2-(methyl orthoacetate) (XXIX) ($CDCl_3$).

(τ4.53). The quartet centered at τ4.90 was assigned to H-3 with the larger spacing (10 Hz) due to the trans diaxial coupling of H-3 with H-4. From the data (Table XI), 3-O-acetyl-β-noviose 1,2-(methyl orthoacetate) (XXVIII) has the methoxyl group oriented exo to the fused ring system (137); that is, the methoxyl group is trans to the pyranose ring. This result is in accordance with the suggestion by Lemieux and Cipera (138) that the high degree of stereoselectivity arose because of an easier approach of the alcohol to the side of the acetoxonium ion shown below which is trans to the pyranose ring.



exo

XXVIII

Table XI

N.m.r. parameters (60 MHz, $CDCl_3$) of β-noviose 1,2-(methyl orthoacetate) (XXIX) and its 3-O-acetyl detivative (XXVIII)

Compound	H-1 (τ)	$J_{1,2}$ (Hz)	H-2 (τ)	$J_{2,3}$ (Hz)	H-3 (τ)	$J_{3,4}$ (Hz)	H-4 (τ)	1'-OCH_3 (τ)	4-OCH_3 (τ)	1'-CH_3 (τ)	$\times^{CH_3}_{CH_3}$ (τ)	OAc (τ)	OH (τ)
XXVIII	4.53	2.5	5.40	4.0	4.90	10	-	6.75	6.46	8.30	8.67, 8.82	7.83	-
XXIX	4.58	2.8	5.56	4.0	6.15	9.5	6.90	6.73	6.42	8.32	8.70, 8.88	-	7.55 $J_{H_3-OH_3} \simeq$ 7.5 Hz

XXVIII 3-O-acetyl-β-noviose 1,2-(methyl orthoacetate)

XXIX β-noviose 1,2-(methyl orthoacetate)

The deacetylation of compound XXVIII with barium methoxide in methanol gave crystalline β-noviose 1,2-(methyl orthoacetate) (XXIX) in 76% yield. The n.m.r. spectrum is shown in Fig. 23. The doublet with a spacing of 7.5 Hz at τ7.55 was assigned to the hydroxyl proton, since it disappeared when the solution was shaken with D_2O. The octet at τ6.15 was assigned to H-3. The appearance of the signal was due to the geminal coupling of H-3 with the hydroxyl proton and vicinal couplings with H-2 and H-3. The signal for H-1 is a doublet with a spacing of 2.8 Hz at τ4.58. The quartet at τ5.56 was assigned to H-2 with the larger spacing (4.0 Hz) arising through coupling of H-2 with H-3. The signal for H-4 is a sharp doublet with a spacing of 9.5 Hz at τ6.90.

β-Noviose 1,2-(methyl orthoacetate) (XXIX) would be a useful intermediate in the syntheses of a variety of aryl 3-O-acyl-α-noviosides because it has the 3-position free. It is recalled that although the antibiotics novobiocin (I) and coumermycin A_1 (II) differ considerably in structure, a coumarin unit is common to both as well as the noviose residue. In both of the antibiotics, the noviose is substituted at the 3-position: by an O-carbamoyl group in the case of novobiocin, and by an

O-(5-methyl-2-pyrrolecarbonyl) group in the case of coumermycin A_1. Thus, it seems that the antibiotic structures can undergo structural modification and retain anti-microbial activity. It is to be noted that these antibiotics possess the sugar molecule glycosidically linked as an α-L-pyranoside. If the synthesis of this α-L-glycoside linkage can be mastered on a broad basis, it is likely that a wide variety of antibiotics would become available and perhaps many with activities superior to those of the natural compounds.

The Koenigs-Knorr reaction (139) was used by Vaterlaus and co-workers in the synthesis of novobiocin (I) (24) from 2,3-O-carbonyl-β-noviosyl chloride (25). 2,3-O-Carbonyl-β-noviosyl chloride was reacted with 4-benzyloxy-7-hydroxy-8-methyl coumarin (13, 14), on catalysis by a silver salt, to give Walden inversion at the anomeric center.

Another general method of glycosidation is via the orthoesters. The reactions of the 1,2-orthoesters of D-glucopyranose with an alcohol and antimony pentachloride provided near quantitative yields of alkyl D-glucopyranosides (140). The ratio of α- to β-isomers was determined by the amount of catalyst used. Kochetkov and co-workers (141) reported the O-glycosidation in which the 1,2-O-alkyl orthoesters led stereospecifically to the 1,2-trans glycosides. They developed a standard procedure which involved the condensation of sugar orthoesters with alcohols

in boiling nitromethane in the presence of mercuric bromide (0.02-0.07 mole per mole of alcohol). The procedure was successfully applied to the synthesis of various compounds containing glycosidic bonds.

Since 3,4,6-tri-O-acetyl-β-D-mannopyranose 1,2-(methyl orthoacetate) (XXX) is quite similar to 3-O-acetyl-β-noviose 1,2-(methyl orthoacetate) (XXVIII) in spatial orientation and is readily available (81), it was used as a model material in the condensation with aromatic hydroxylic compounds. Franks and Montgomery (142) investigated the acid-catalyzed ring opening of 3,4,6-tri-O-benzyl-β-D-mannopyranose 1,2-(methyl orthoacetate) in methylene chloride containing p-toluenesulfonic acid, excluding water or any alcohol, and found that complete rearrangement occurred within 20 min at 46.5°, with almost exclusive formation of derivatives of methyl α-D-mannopyranoside. Methyl 2-O-acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranoside and methyl 3,4,6-tri-O-benzyl-α-D-mannopyranoside were isolated in 82% and 7% yield, respectively. A small proportion of methyl 3,4,6-tri-O-benzyl-β-D-mannopyranoside was identified by t.l.c. The presence of methanol in the reaction mixture appeared to have little or no effect upon the direction of the ring opening, but there was more extensive loss of the 2-acetoxy group.

The condensation of compound XXX (1.0 mole) with phenol (2.0 moles) in methylene chloride containing antimony pentachloride (0.05 mole) gave a reaction mixture which consisted of five components as indicated by the thin-layer chromatogram (Fig. 24). The mixture was separated by column chromatography on Silica Gel G and the four major components were identified by n.m.r. as phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI), methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII), phenyl 3,4,6-tri-O-acetyl-α-D-mannopyranoside, and methyl 3,4,6-tri-O-acetyl-α-D-mannopyranoside. Acetylation of the latter two compounds gave XXXI and XXXII, respectively.

Compound XXXI was obtained as a syrup which was induced to crystallize from 98% ethanol by seeding with an authentic sample prepared by the Helferich method (83); m.p. 79-80°, $[\alpha]_D^{26}$ +70.5° (c, 1.40 in chloroform). [Literature (82), m.p. 79-80°, $[\alpha]_D$ + 74.9° (chloroform)]. The n.m.r. spectrum of phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI) is shown in Fig. 25. The signals at τ4.40-4.83, integrated as four protons, were assigned to H-1, H-2, H-3 and H-4. The signals for H-5, H-6 and H-6' are at τ5.70-6.16. Four distinct acetoxy signals were observed at τ7.87, 8.01, 8.05 and 8.09. the signal at τ7.87 was assigned to the axial 2-acetoxy protons (45).

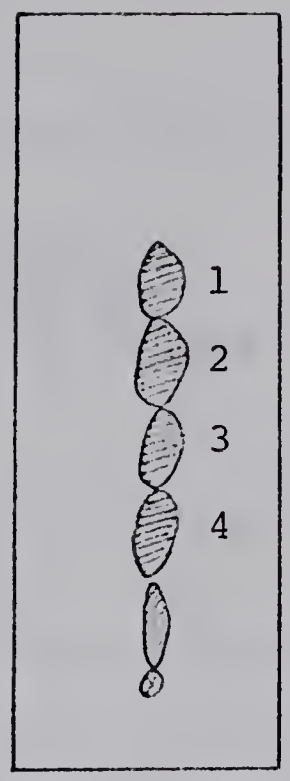


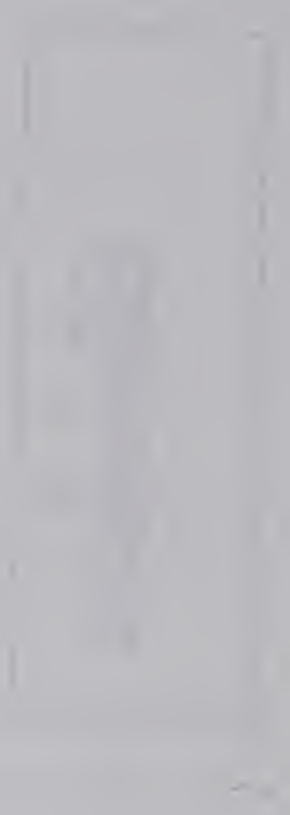
Fig. 24. A thin-layer chromatogram of the condensation product of 3,4,6-tri-O-acetyl-β-D-mannopyranose 1,2-(methyl orthoacetate) (XXX) with phenol using 50% ethyl acetate in toluene as the developing solvent.

1 phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI)

2 methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII)

3 phenyl 3,4,6-tri-O-acetyl-α-D-mannopyranoside

4 methyl 3,4,6-tri-O-acetyl-α-D-mannopyranoside



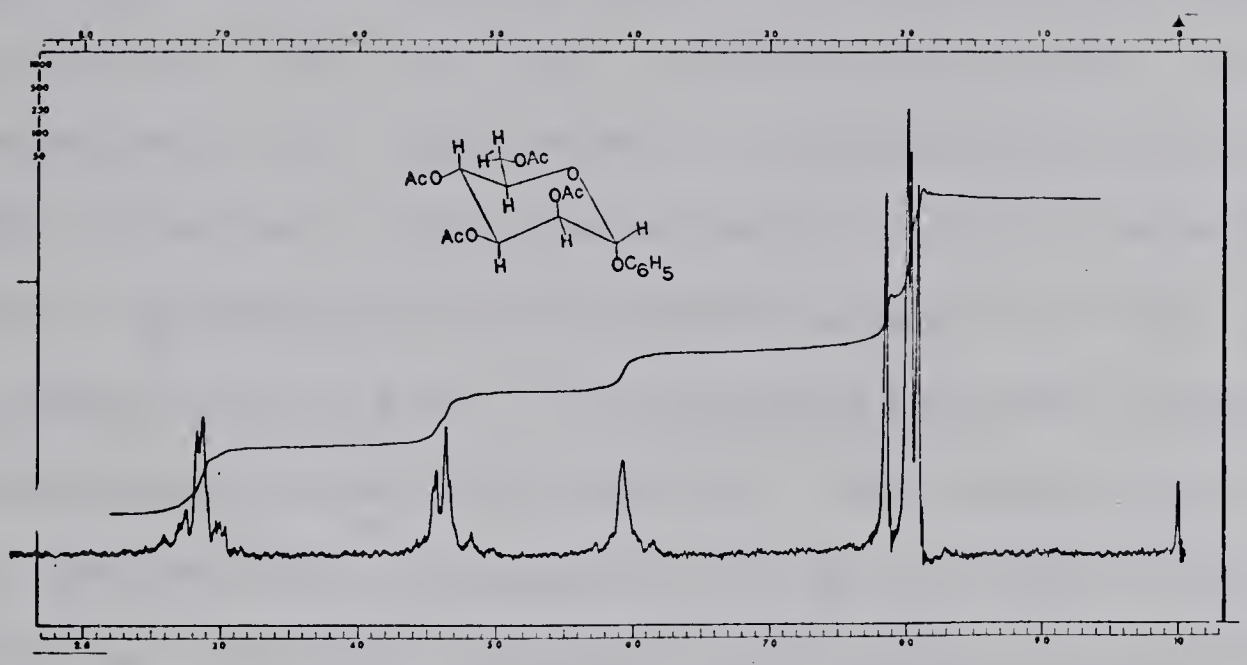


Fig. 25. N.m.r. spectrum (60 MHz) of phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI) (CCl_4).

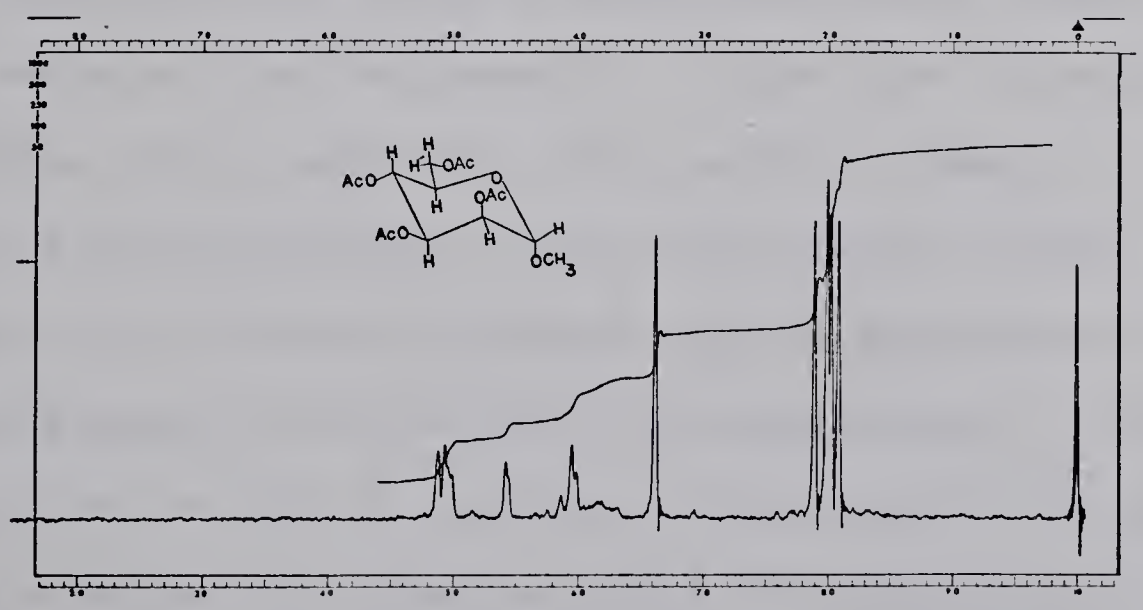


Fig. 26. N.m.r. spectrum (60 MHz) of methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII) (CCl_4).





Methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII) was obtained as a crystalline mass. Recrystallization from 95% ethanol afforded pure material m.p. 63-64°, $[\alpha]_D^{26}$ +45° (c, 1.36 in chloroform). The melting point was undepressed in admixture with authentic XXXII. The n.m.r. spectrum of methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII) is shown in Fig. 26. The signals at τ4.84-5.03, integrated as three protons, were assigned to H-2, H-3 and H-4. The signal for H-1 is a doublet with a spacing of 1.5 Hz at τ5.43. The quartet at τ5.81 was assigned to H-6 with $J_{5,6} \simeq 5.0$ Hz and $J_{6,6'} \simeq 12$ Hz. The signal for H-6' was at τ6.05 with $J_{5,6'} \simeq 2.0$ Hz. The multiplet centered at τ 6.19 was assigned to H-5.

Acetylation of the condensation product gave mainly two compounds as indicated by a thin-layer chromatogram. From the n.m.r. spectrum, the yields of phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI) and methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII) were estimated to be 55 and 45%, respectively. Increasing the concentration of antimony pentachloride did not seem to alter the relative yield of compounds XXXI and XXXII, but more discoloration of the solution was observed. However, when 20 moles of phenol per mole of the orthoester (XXX) was used, the relative yield of compounds XXXI and XXXII was calculated to be 87:13. The n.m.r.

spectrum of this mixture is shown in Fig. 27. The ratio was found by comparison of the integration values for the signals of the phenyl ring protons at τ2.56-3.17 in compound XXXI and the methoxyl protons at τ6.63 in compound XXXII.

The condensation of compound XXX (1.0 mole) with phenol (2.0 moles) in boiling nitromethane containing mercuric bromide (0.05 mole) afforded phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI) and methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII) in the ratio of 15:85. The n.m.r. spectrum of this mixture is shown in Fig. 28. When p-toluenesulfonic acid was used as the catalyst in methylene chloride, the acetylated condensation product consisted of at least four spots as indicated by the chromatogram of which the two fastest compounds were XXXI and XXXXII, respectively. The n.m.r. spectrum indicated the presence of some tosyl derivative which had signals centered at τ2.2, 2.65 and 7.55. The ratio of XXXI, XXXII and the sugar tosylate , was calculated to be 69:13:18. The formation of the sugar tosylate was also observed in the glycosidation of the 1,2-orthosesters of D-glucopyranose with simple aliphatic alcohols using p-toluenesulfonic acid as the catalyst (140). Fusion of compound XXX and phenol without a catalyst at 160° for 1 h provided XXXI and XXXII in the ratio of 47:21 with 32% of the unreacted starting material.

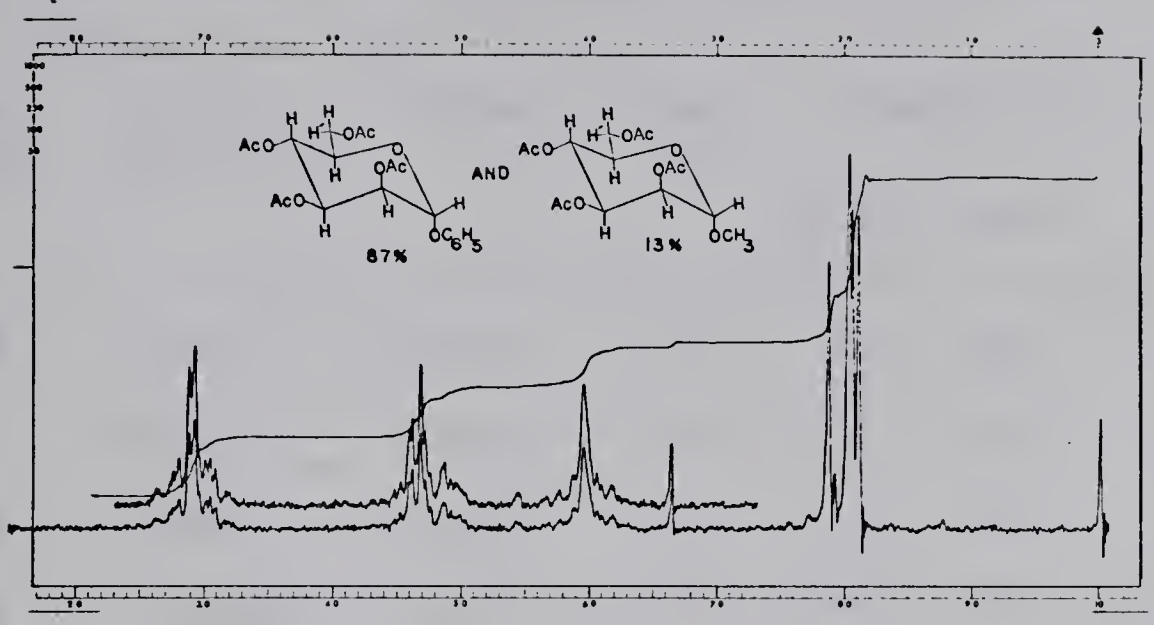


Fig. 27. N.m.r. spectrum (60 MHz) of a mixture of compounds XXXI and XXXII in the ratio of 87:13 (CCl_4).

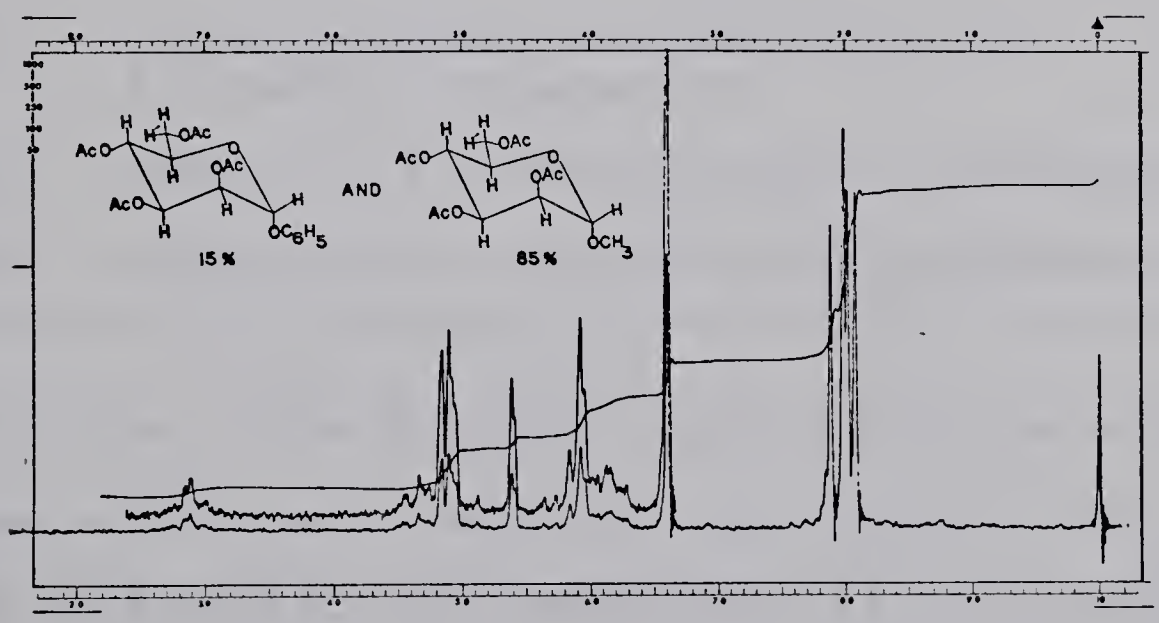


Fig. 28. N.m.r. spectrum (60 MHz) of a mixture of compounds XXXI and XXXII in the ratio of 15:85 (CCl_4).

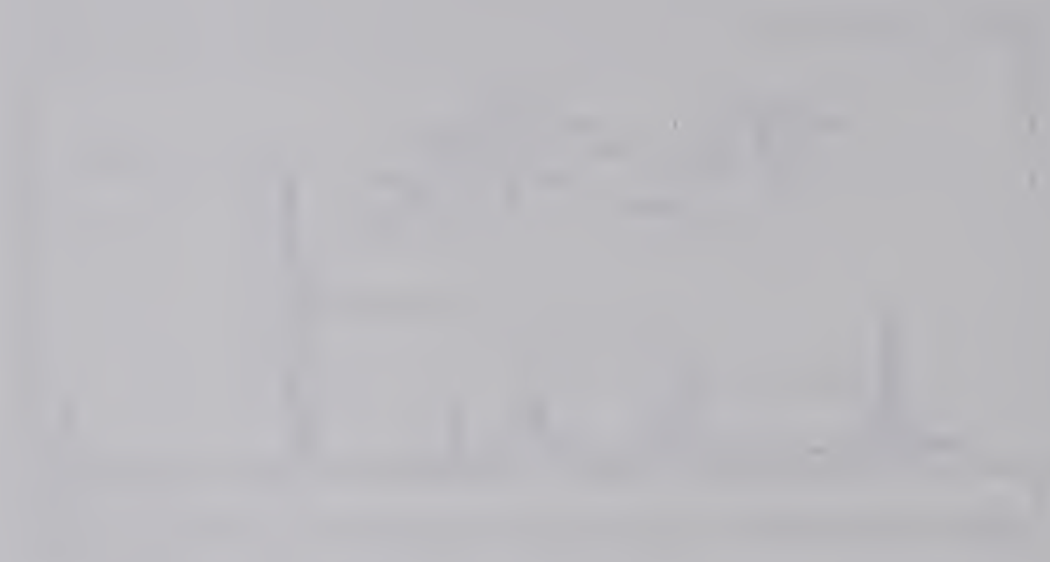




Table XII

Yields in the formation of α-D-mannopyranosides from 3,4,6-tri-O-acetyl-β-D-mannopyranose 1,2-(methyl orthoacetate) (XXX) (1.0 mole)

phenol, moles	Catalyst, 0.05 mole	Solvent	Time, h	Yield (n.m.r.) XXXI	XXXII	others
2.0	$SbCl_5$	CH_2Cl_2	0.5	55	45	-
20	$SbCl_5$	CH_2Cl_2	0.5	87	13	-
2.0	$HgBr_2$	CH_3NO_2	1.5	15	85	-
2.0	P-TsOH	CH_2Cl_2	24	69	13	18 (sugar tosylate)
2.0	-	Fusion, 160°	1	47	21	32 (XXX)

XXX 3,4,6-tri-O-acetyl-β-D-mannopyranose 1,2-(methyl orthoacetate)

XXXI phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside

XXXII methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside

In view of the different products obtained under various conditions it seems that more than one mechanism can be envisaged for the condensation of 3,4,6-tri-O-acetyl-β-D-mannopyranose 1,2-(methyl orthoacetate) (XXX) with phenol in the presence of an acid catalyst (Fig. 41). The conversion of the orthoester (XXX) into methyl mannosides indicates that preliminary splitting out of methanol must have occurred.

Fig. 41. Possible mechanisms in the formation of α-D-mannopyranosides

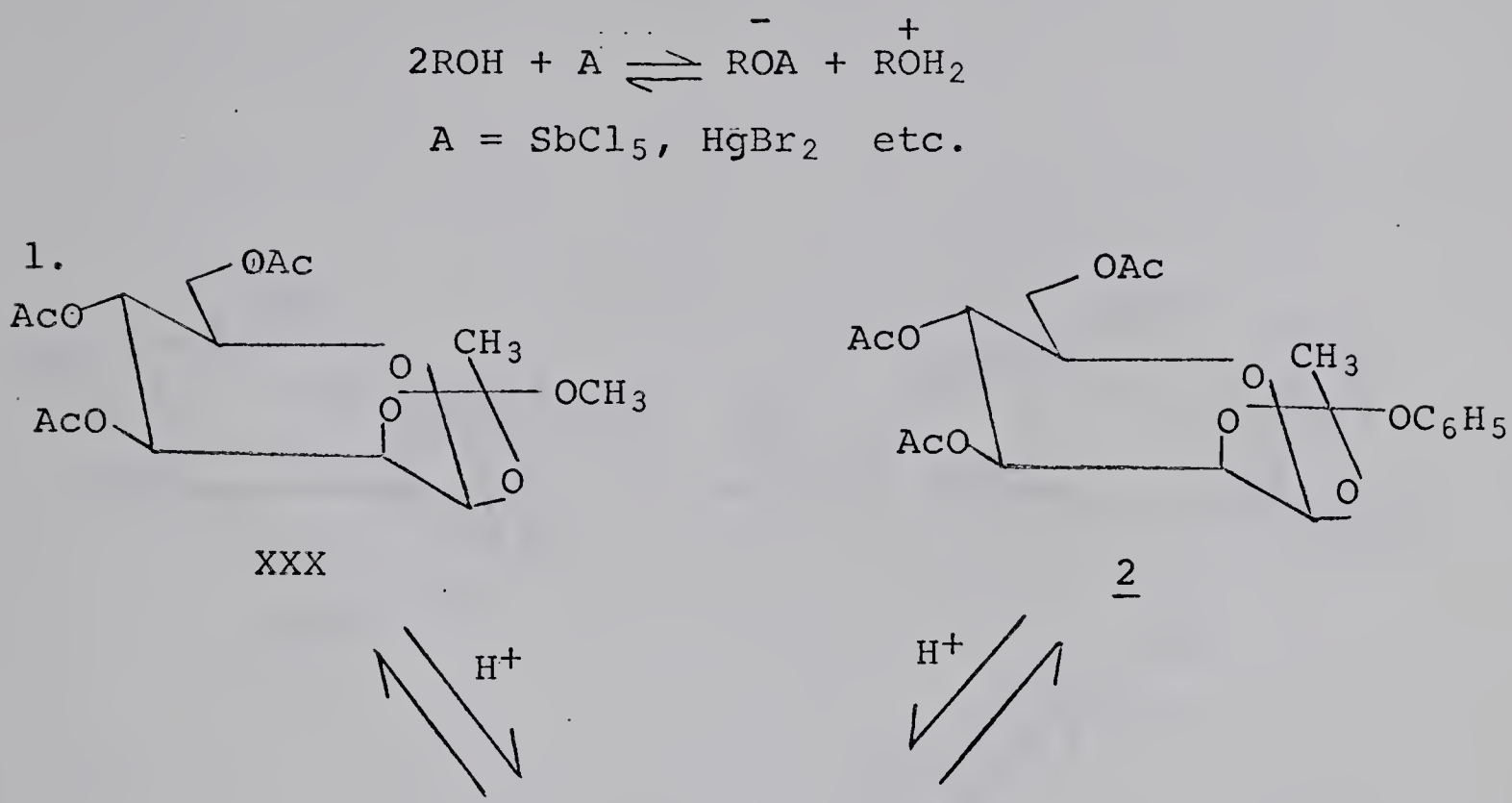
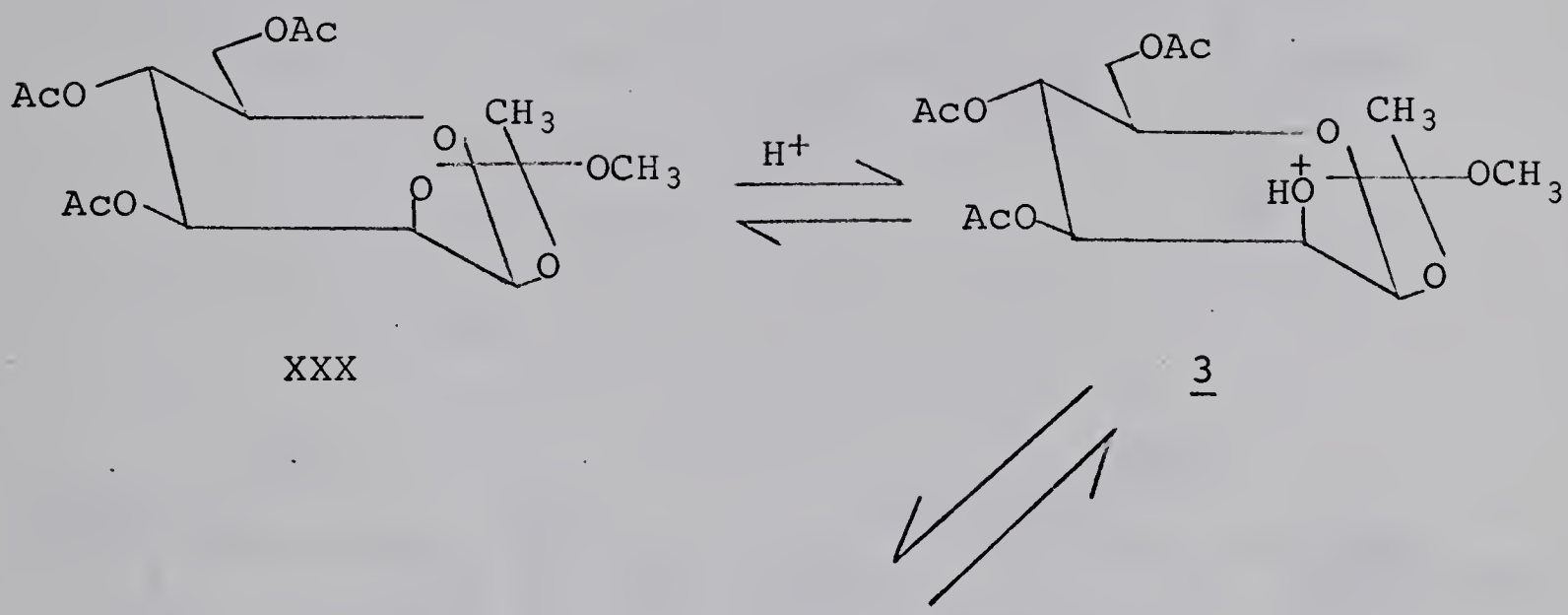


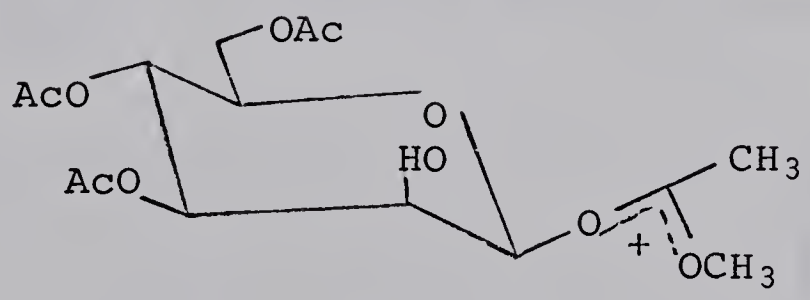
Fig. 41 (cont'd)

2.

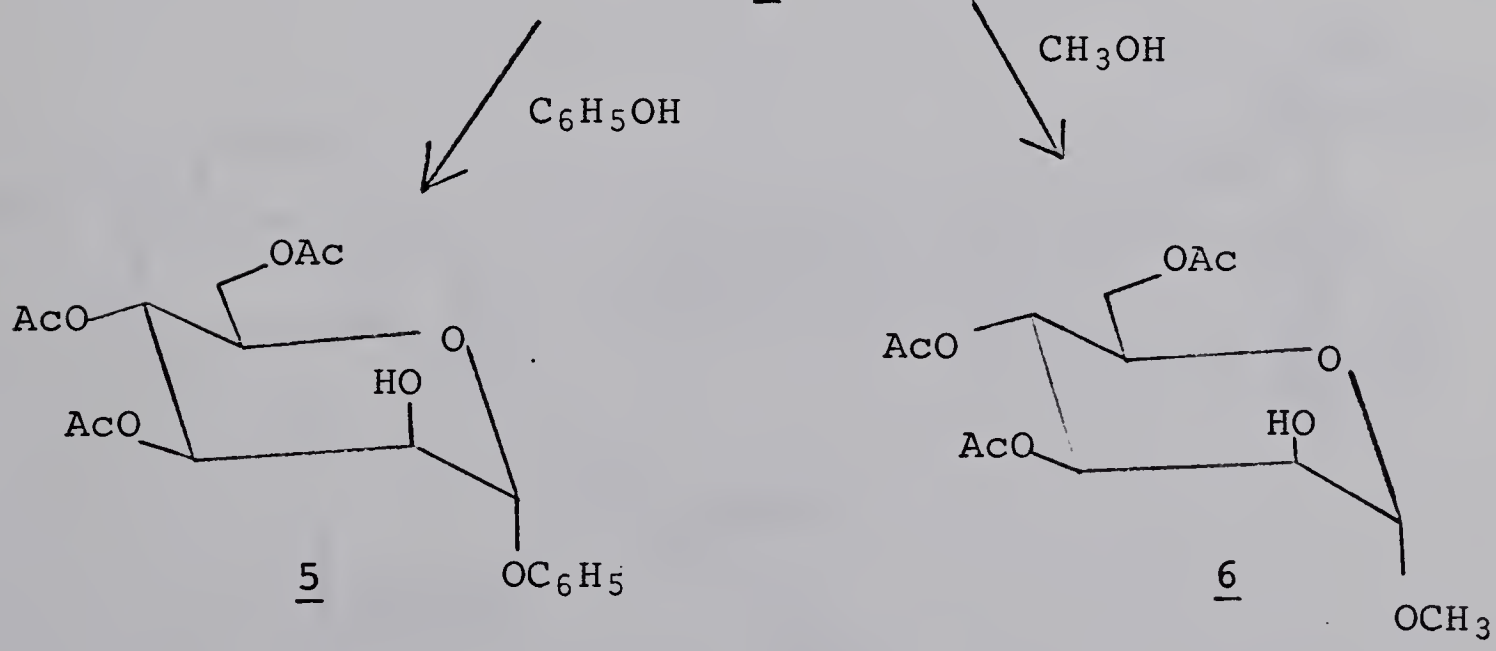


XXX

3



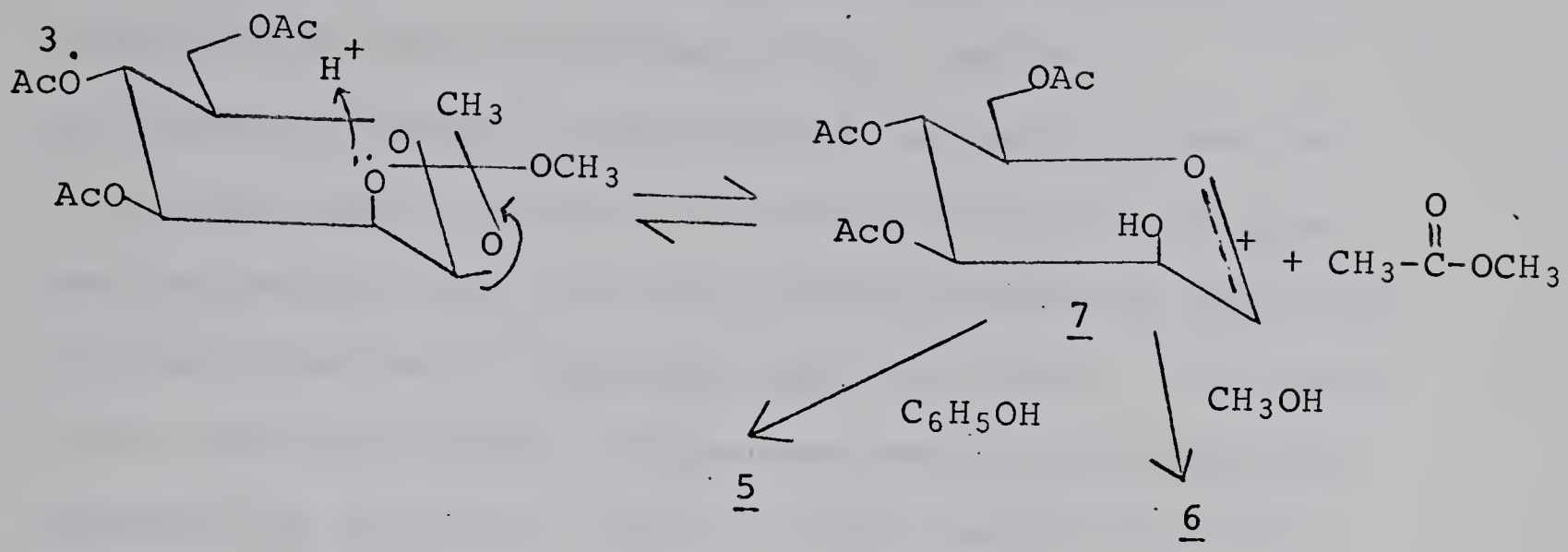
4

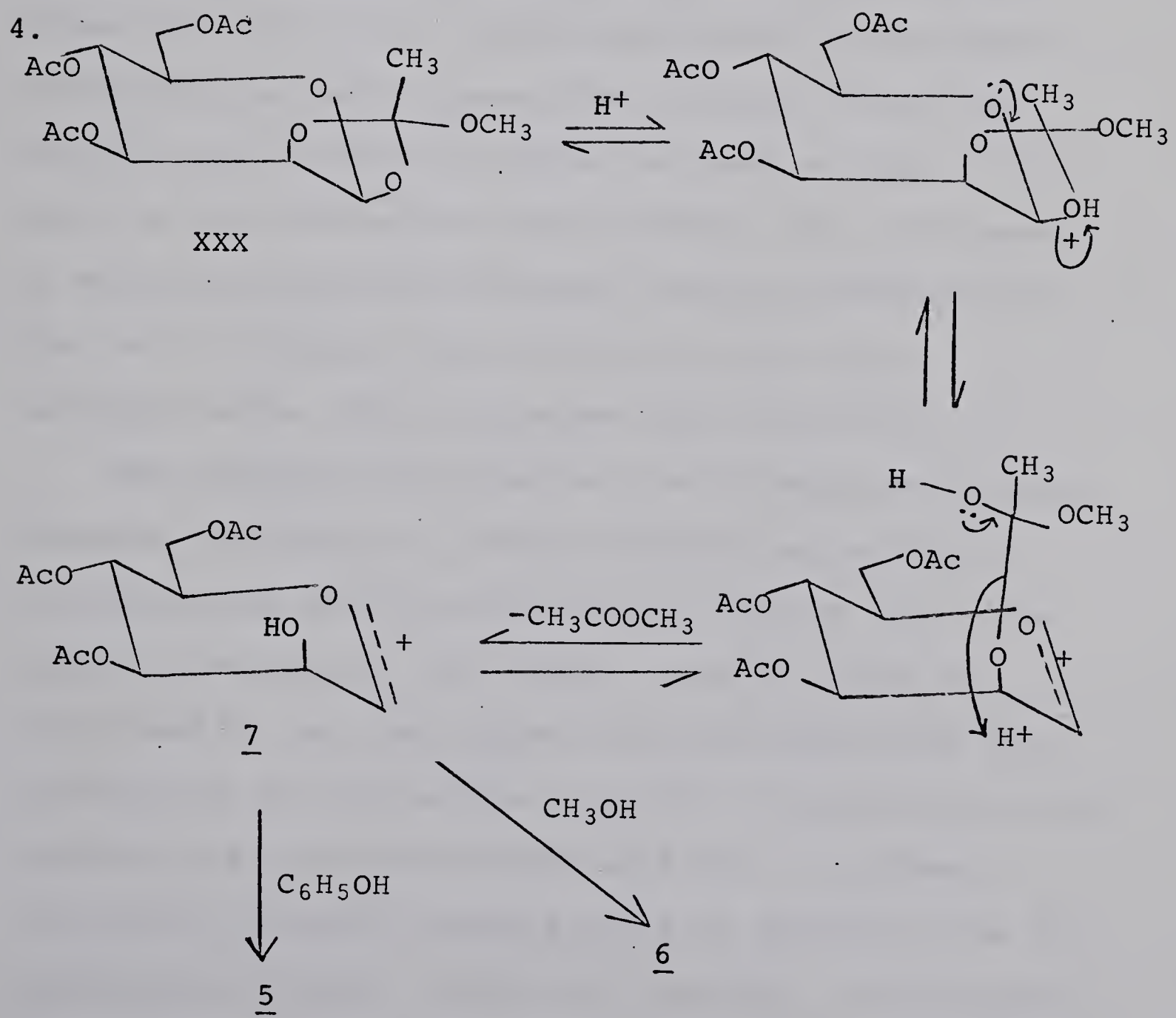


5

6

Fig. 41 (cont'd)


3.
OAc
AcO
H+
CH3
O
OCH3
AcO
O
O
AcO
OAc
AcO
O
HO
+
O
+ CH3-C-OCH3
7
C6H5OH
CH3OH
5
6


4.
OAc
AcO
CH3
O
AcO
O
OCH3
O
XXX
H+
OAc
AcO
O
CH3
O
OCH3
AcO
O
OH
+
H
CH3
O
OCH3
OAc
AcO
AcO
O
O
+
H+
-CH3COOCH3
OAc
AcO
O
HO
+
AcO
7
CH3OH
C6H5OH
5
6

The first step of the glycosidation should be the formation of the acetoxonium ion (1) (Route 1). Nucleophilic attack by the alcohol can occur either on the electrophilic orthoester carbon giving rise to the new orthoester (2), or on the glycosidic center resulting in the formation of compounds XXXI and XXXII. This seems to be the only possible route when mercuric bromide was used as the catalyst, since 2, 3 and 4 would result in the loss of methyl acetate. Since methanol, which was split off from the orthoester (XXX), was present as well as phenol (added) in the reaction medium, the glycosidation undoubtedly became a competitive reaction. This was evident when 20 moles of phenol was used in place of 2.0 moles in the condensation with compound XXX (1.0 mole) in methylene chloride containing antimony pentachloride, the yield of phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI) increased from 55 to 87%.

The formation of compounds 5 and 6 may have occurred from the intermediate 4 (Route 2) which was probably in equilibrium with the protonated orthoester (3). The cyclic carbonium ion (7) (Routes 3 and 4), which is stabilized by the ring oxygen, has been postulated as an intermediate in the reaction of alkyl 1,2-orthoesters with alcohols and p-toluenesulfonic acid (57). In these reactions, the major products would be expected to be the α-D-mannopyranosides. Since the formation of the cyclic carbonium ion (7) involves the loss of methyl acetate,

routes 3 and 4 could also explain the presence of compounds 5 and 6.

The condensation of 3-O-acetyl-β-noviose 1,2-(methyl orthoacetate) (XXVIII) (1.0 mole) with phenol (2.0 moles) in methylene chloride containing antimony pentachloride (0.05 mole), and followed by acetylation gave a reaction mixture which consisted of three compounds as indicated by the thin-layer chromatogram (Fig. 29). The mixture was separated by chromatography and identified by n.m.r. as phenyl 2,3-di-O-acetyl-α-novioside (XXXIII), methyl 2,3-di-O-acetyl-α-novioside (XXXIV), and methyl 2,3-di-O-acetyl-β-novioside (XXXV), respectively. The ratio of the yields of XXXIII and XXXIV + XXXV was estimated to be 15:85. This figure was found by comparison of the integration values for the signals of the phenyl ring protons at τ2.78-3.25 in compound XXXIII and the 1-methoxyl protons at τ6.65 in compounds XXXIV and XXXV. Judging from the intensity of the spots on t.l.c., compound XXXIV was formed in a larger proportion than XXXV. This result is different from that obtained when 3,4,6-tri-O-acetyl-β-D-mannopyranose 1,2-(methyl orthoacetate) (XXX) was used as the orthoester. As shown in Table XII, under the same conditions phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI) was formed to the extent of 55%.

Phenyl 2,3-di-O-acetyl-α-novioside (XXXIII) had $[\alpha]_D^{26}$ -42.5° (c, 2.37 in chloroform); the n.m.r. spectrum

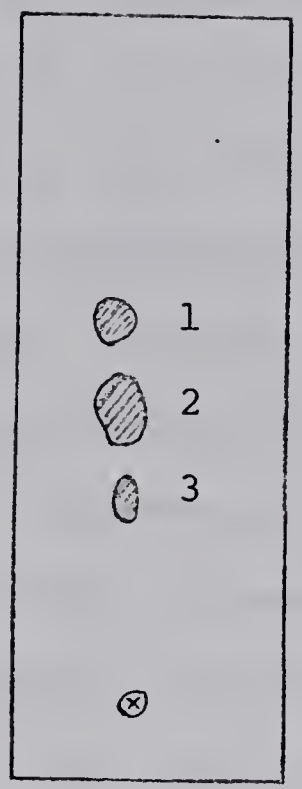


Fig. 29. A thin-layer chromatogram of the condensation product of 3-O-acetyl-β-noviose 1,2-(methyl orthoacetate) (XXVIII) with phenol, using 20% ethyl acetate in toluene as the developing solvent

1 phenyl 2,3-di-O-acetyl-α-novioside (XXXIII)

2 methyl 2,3-di-O-acetyl-α-novioside (XXXIV)

3 methyl 2,3-di-O-acetyl-β-novioside (XXXV)

of this compound is shown in Fig. 30. The signal for H-4 is a sharp doublet with a spacing of 10 Hz at τ6.70. The quartet at τ4.58 was assigned to H-3 with the smaller spacing (3.0 Hz) arising through the coupling of H-3 with H-2. The signal for the anomeric proton is a doublet with a spacing of 2.0 Hz at τ4.67. The signal centered at τ4.71 was assigned to H-2. The shape of the signal for H-2 indicates the presence of second-order effects from virtual long-range coupling. This was due to the small difference in chemical shifts for H-1, H-2 and H-3. The signal for H-3 (τ4.58) was at a lower field than that of H-2 (τ4.71). This is because of the deshielding effect of the axial phenoxy group at C-1 (113, 114). This fact coupled with the large negative rotation of compound XXXIII confirmed the assignment of the phenyl 2,3-di-O-acetylnovioside as the α-anomer.

The n.mr. spectra of the α- and β-anomers of methyl 2,3-di-O-acetylnovioside are shown in Fig. 31 and 32, respectively. For the α-anomer (XXXIV), the signal for H-4 is a sharp doublet with a spacing of 10 Hz at τ6.76. Irradiation at this resonance frequency collapsed the quartet at τ4.81 to a doublet with the smaller spacing (3.0 Hz). Therefore the signal for H-3 must be at this position and the spacing (3.0 Hz) is the coupling constant of H-3 with H-2. The quartet at τ4.94 was assigned to H-2 with the smaller spacing (1.7 Hz) arising through the coupling of H-2 with H-1. The signal for the anomeric proton is a doublet at

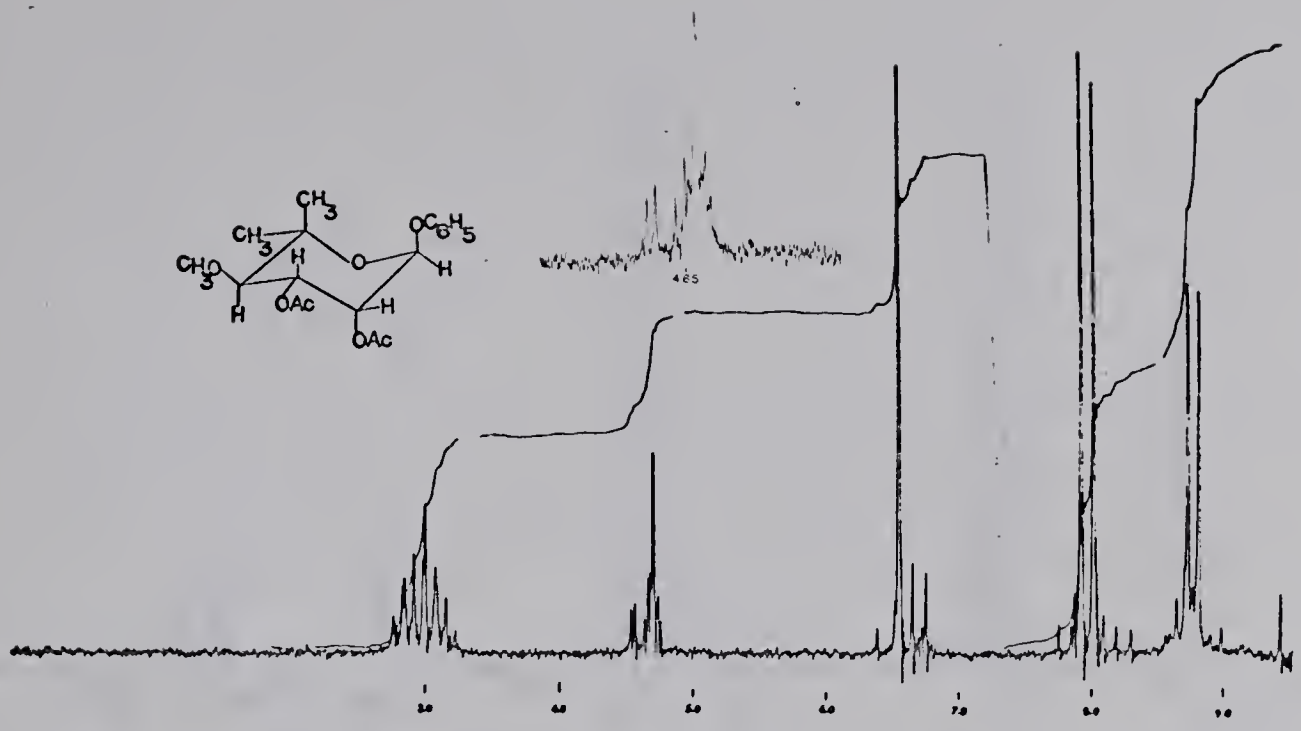


Fig. 30. N.m.r. spectrum (100 MHz) of phenyl 2,3-di-O-acetyl-α-novioside (XXXIII) (CCl_4).

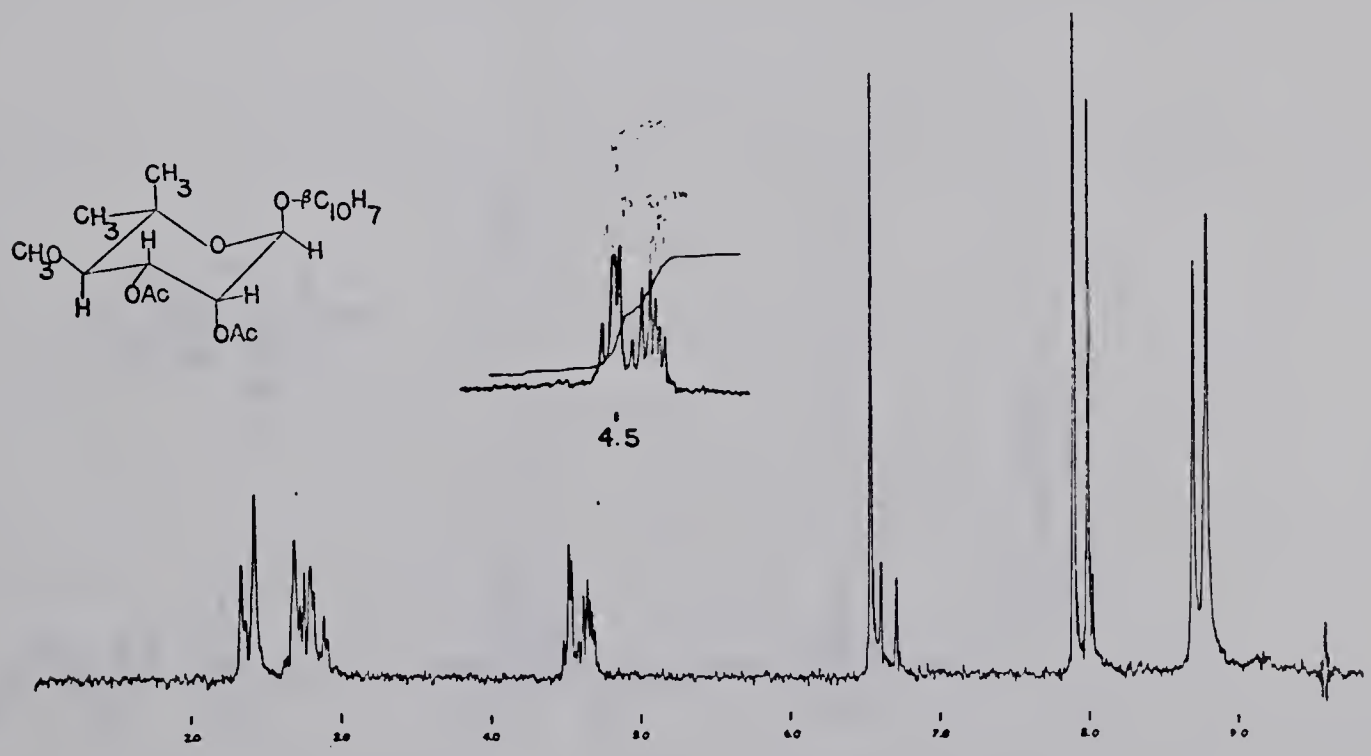


Fig. 36. N.m.r. spectrum (100 MHz) of β-naphthyl 2,3-di-O-acetyl-α-novioside (XXXVI) (CCl_4).



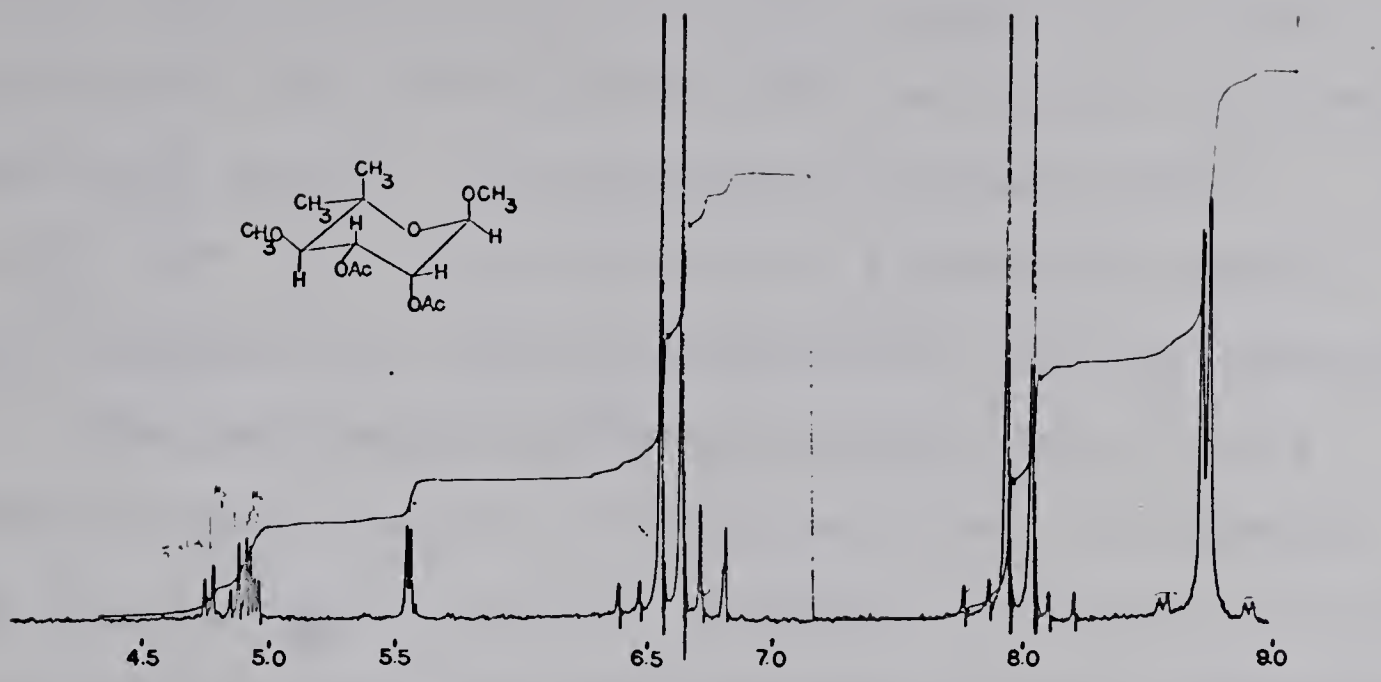


Fig. 31. N.m.r. spectrum (100 MHz) of methyl 2,3-di-O-acetyl-α-novioside (XXXIV) (CCl_4).

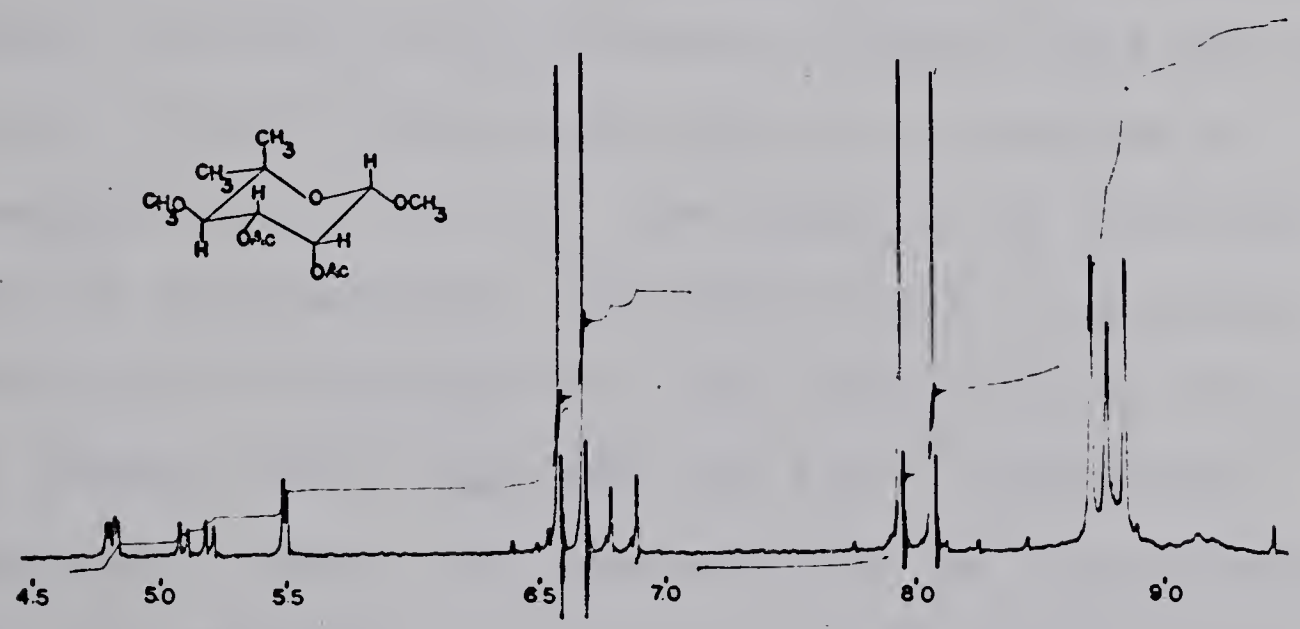
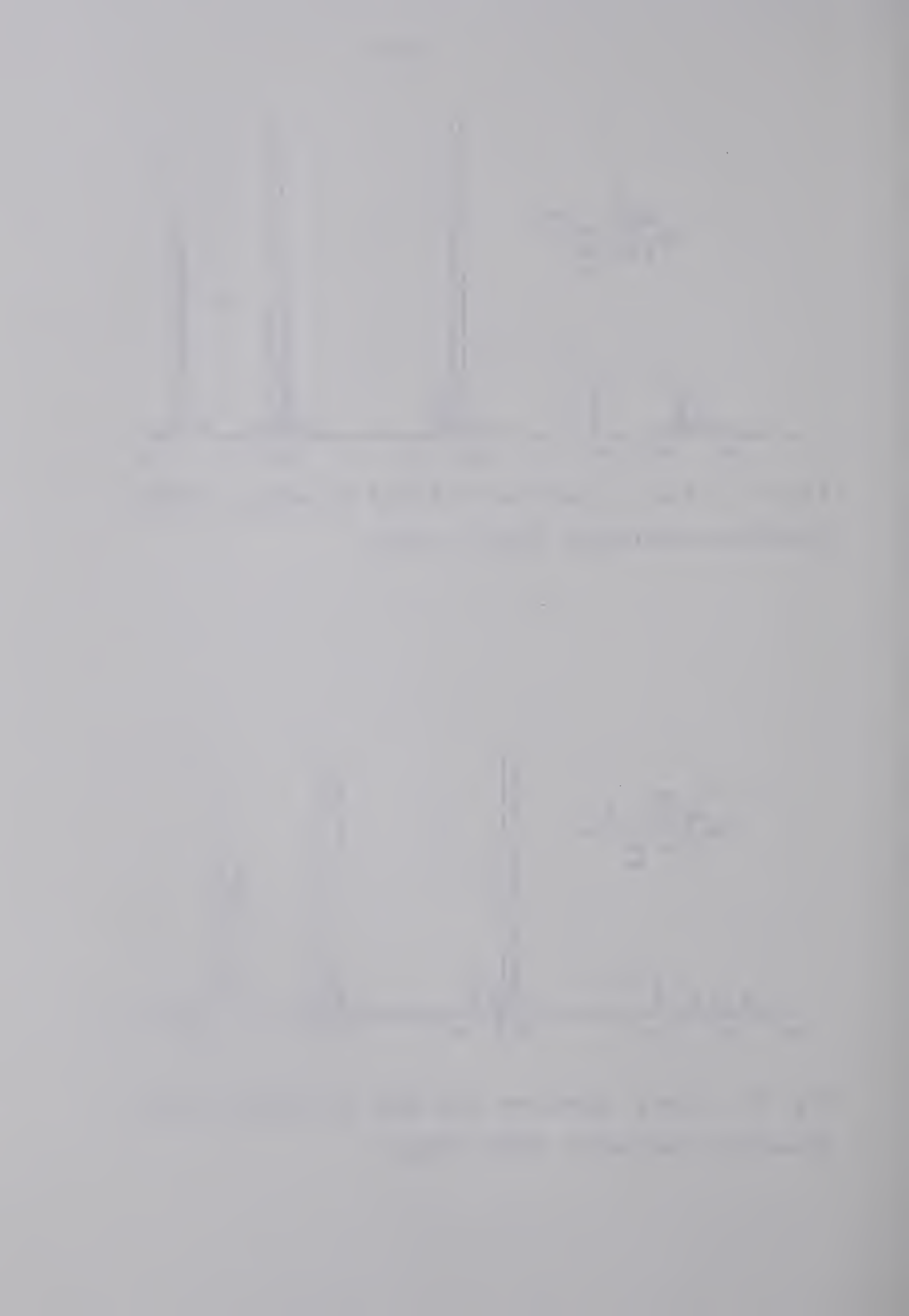


Fig. 32. N.m.r. spectrum (100 MHz) of methyl 2,3-di-O-acetyl-β-novioside (XXXV) (CCl_4).



τ5.55. The signal for H-3 (τ4.81) was again at a lower field than that of H-2 (τ4.94) for the reasons which were mentioned earlier. the rotation of compound XXXIV, $[\alpha]_D^{26}$ -18° (c, 1.59 in chloroform) appeared to support the assignment of the α-L-configuration for this compound.

For the β-anomer (XXXV), the signal for H-1 is a doublet with a spacing of 1.3 Hz at τ5.49. Irradiation at this resonance frequency collapsed the quartet at τ4.81 to a doublet with the larger spacing (3.0 Hz). Therefore, the signal for H-2 must be at this position and the spacing (3.0 Hz) is the coupling constant of H-2 with H-3. The quartet at τ5.15 was assigned to H-3 with the larger spacing (10 Hz) arising through the coupling of H-3 with H-4. The signal for H-4 is a sharp doublet at τ6.84. The signal for H-3 (τ5.15) is now at a higher field than that of H-2 (τ4.81) (compare with the n.m.r. spectrum of compound XXXIV, Fig. 31). The signal at τ8.77 was not part of compound XXXV. And unfortunately, its origin could not be accounted for. The large positive rotation of compound XXXV, $[\alpha]_D^{26}$ +48° (c, 0.8 in chloroform) appeared to support the assignment of the β-L-configuration for this compound.

Deacetylation of compounds XXXIV and XXXV with barium methoxide in absolute methanolgave the methyl α- and β-novioside, respectively. The n.m.r. spectra of the latter two compounds are shown in Fig. 33 and 34.

Table XIII

N.m.r. parameters (100 MHz, CCl_4) of some novioside diacetates

Compound	H-1 (τ)	$J_{1,2}$ (Hz)	H-2 (τ)	$J_{2,3}$ (Hz)	H-3 (τ)	$J_{3,4}$ (Hz)	H-4 (τ)	4-OCH_3 (τ)	1-OCH_3 (τ)	C_6H_5, or β-$C_{10}H_7$ (τ)	ax-OAc (τ)	eq-OAc (τ)	$\diagup\!\!\diagdown^{CH_3}_{CH_3}$ (τ)
XXXIII	4.67	2.0	4.71	3.0	4.58	10	6.70	6.54	-	2.78-3.25	7.90	8.0	8.72, 8.80
XXXIV	5.55	1.7	4.94	3.0	4.81	10	6.76	6.55	6.63	-	7.93	8.03	8.71, 8.74
XXXV	5.49	1.3	4.81	3.0	5.15	10	6.84	6.57	6.67	-	7.94	8.07	8.71, 8.84
XXXVI	4.50	2.0	4.65	3.0	4.52	10	6.64	6.52	-	2.30-2.92	7.89	7.99	8.69, 8.78

XXXIII phenyl 2,3-di-O-acetyl-α-novioside

XXXIV methyl 2,3-di-O-acetyl-α-novioside

XXXV methyl 2,3-di-O-acetyl-β-novioside

XXXVI β-naphthyl 2,3-di-O-acetyl-α-novioside

When DMSO-d_6 was used as the solvent, the couplings of the hydroxyl protons with geminal hydrogens could be observed clearly. For methyl α-novioside, the two doublets at τ5.13 and 5.29 were assigned to the hydroxyl protons since they disappeared when the solution was shaken with D_2O. The O-deuterated methyl α-novioside gave a much simplified spectrum. The signal for the anomeric proton is a doublet with a spacing of 2.0 Hz at τ5.49. Irradiation at this resonance frequency collapsed the quartet at τ6.33 to a doublet with the larger spacing (3.3 Hz). Therefore, the signal for H-2 must be at this position and the spacing (3.3 Hz) is the coupling constant of H-2 with H-3. The quartet at τ6.22 was assigned to H-3 with the larger spacing (9.0 Hz) arising through the coupling of H-3 with H-4. The signal for H-4 is a sharp doublet at τ6.80.

For methyl β-novioside, the two doublets at τ5.43 and 5.54 were assigned to the hydroxyl protons since they disappeared when the solution was shaken with D_2O. The O-deuterated methyl β-novioside also gave a simplified spectrum. The signal for H-1 is a doublet at τ5.57 with $J_{1,2}$ ≈1.0 Hz. The quartet at τ6.30 was assigned to H-2 with the larger spacing (3.2 Hz) arising through the coupling of H-2 with H-3. The signal for H-4 is a sharp doublet with a spacing of 10 Hz at τ6.93. The quartet at τ6.45 was assigned to H-3.

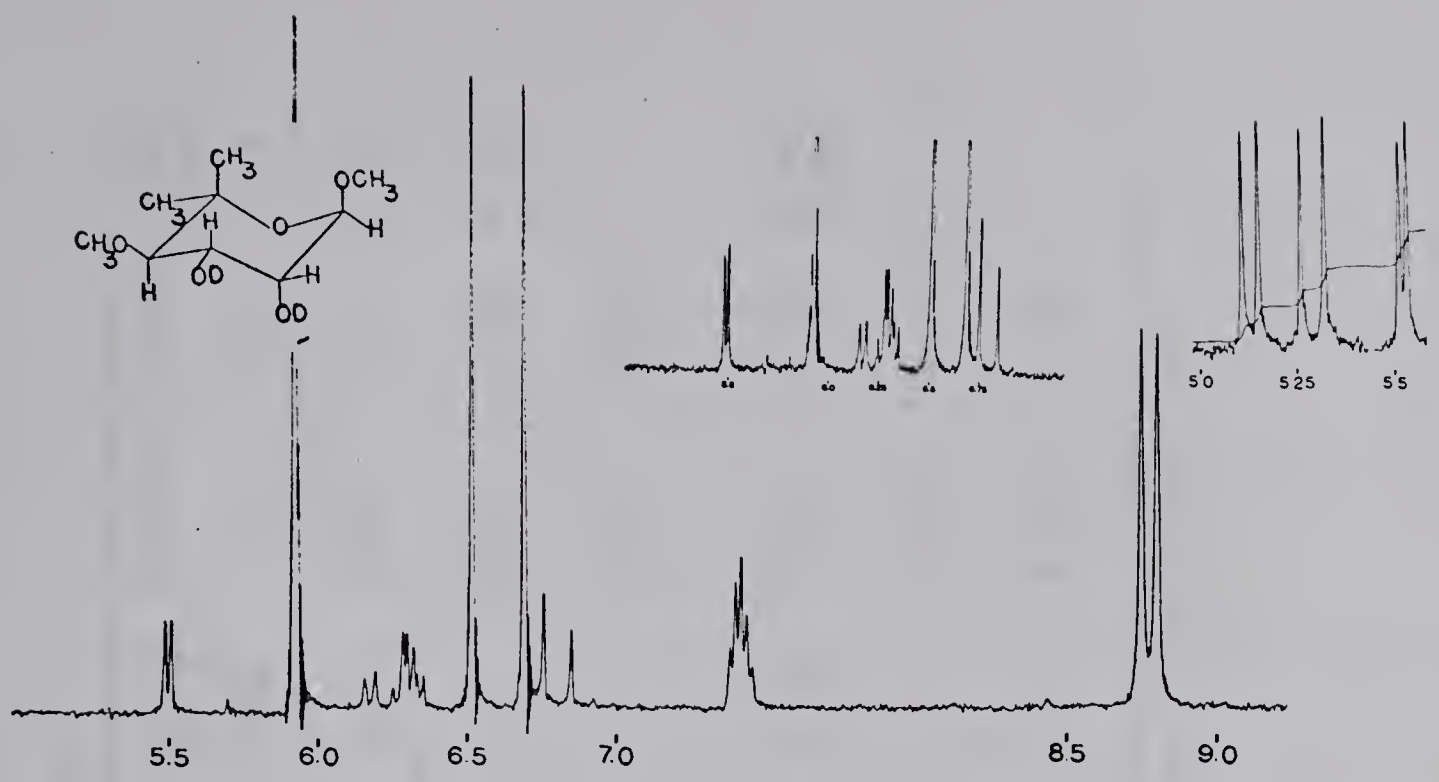


Fig. 33. N.m.r. spectrum (100 MHz) of the O-deuterated methyl α-novioside (DMSO-d_6). Inset with integration, methyl α-novioside (100 MHz) (DMSO-d_6).

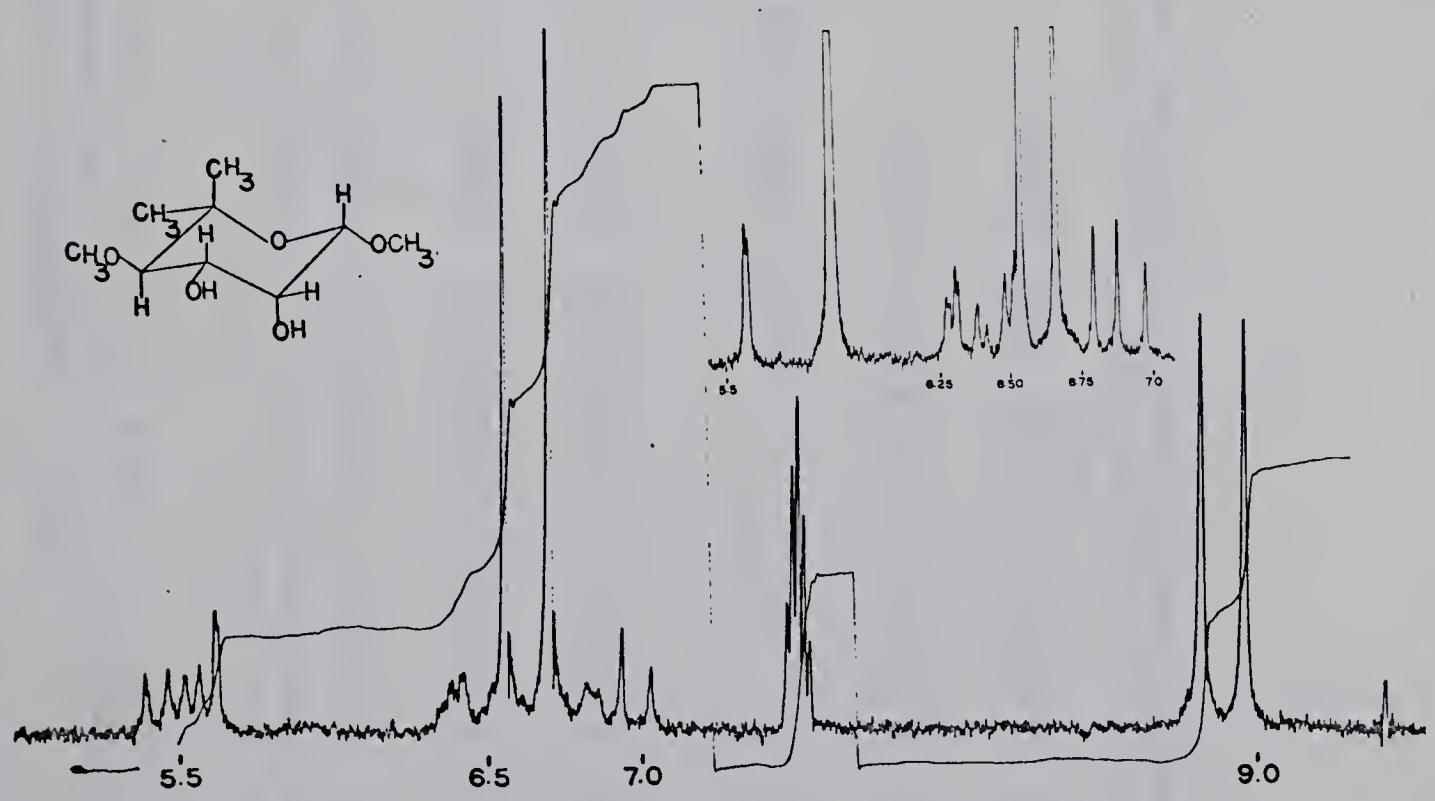


Fig. 34. N.m.r. spectrum (100 MHz) of methyl β-novioside (DMSO-d_6). Inset, the O-deuterated methyl β-novioside (100 MHz) (DMSO-d_6).



Table XIV

N.m.r. parameters of methyl noviosides

Compound	H-1 (τ)	$J_{1,2}$ (Hz)	H-2 (τ)	$J_{2,3}$ (Hz)	H-3 (τ)	$J_{3,4}$ (Hz)	H-4 (τ)	O-H_2 (τ)	$J_{OH_2-H_2}$ (Hz)	OH_3 (τ)	$J_{OH_3-H_3}$ (Hz)	4-OCH_3 (τ)	1-OCH_3 (τ)	$\times^{CH_3}_{CH_3}$ (τ)
α-anomer in DMSO	5.53	2.0	6.38	3.3	6.26	9.0	6.83	5.13	4.2	5.29	6.0	6.52	6.71	8.78, 8.81
"", D_2O added	5.49	2.0	6.33	3.3	6.22	9.0	6.80	-	-	-	-	6.51	6.68	8.74, 8.80
α-anomer in pyr.*	4.94	1.9	5.59	3.2	5.50	8-9	6.22	-	-	-	-	6.31	6.60	-
β-anomer in DMSO	5.62	1.0	-	-	-	9.5	6.98	5.54	4.5	5.43	7.3	6.55	6.69	8.81, 8.96
"", D_2O added	5.57	1.0	6.30	3.2	6.45	10	6.93	-	-	-	-	6.54	6.64	-
β-anomer in pyr.*	5.34	1.0	5.72	3.0	5.8-6.0	8-9	6.36	-	-	-	-	6.30	6.49	-

* Data for the methyl noviosides in pyridine were taken from the literature (42).

The n.m.r. data of both the acetylated and deacetylated noviosides are consistent in that the α-anomers led to a greater deshielding of the 3-proton by the axial aglycon at the C-1 positon (113, 114). The signals for H-3, in every case, were at a lower field than that of H-2. In the case of their β-anomers the signals for H-3 were at a higher field than those of H-2.

The condensation of 3-O-acetyl-β-noviose 1,2-(methyl orthoacetate) (XXVIII) (1.0 mole) with phenol (2.0 moles) in boiling nitromethane containing mercuric bromide (0.05 mole) gave a reaction mixture which consisted of three components as indicated by the thin-layer chromatogram (Fig. 29). The yield of phenyl 2,3-di-O-acetyl-α-novioside (XXXIII) was estimated to be 18%. Judging from the intensity of the spots on t.l.c., methyl 2,3-di-O-acetyl-α-novioside (XXXIV) was again formed in a larger proportion than methyl 2,3-di-O-acetyl-β-novioside (XXV). From the above results, it appeared that changing the acid catalyst from antimony pentachloride to mercuric bromide did not alter the yield of phenyl 2,3-di-O-acetyl-α-novioside (XXXIII) (15-18%). However, when 20 moles of phenol per mole of the orthoester (XXVIII) was used, the yield of compound XXXIII was doubled (36%).

When β-naphthol was condensed with the orthoester (XXVIII) in boiling nitromethane containing mercuric bromide, a reaction mixture which consisted of at least four

Table XV

Yields in the formation of 2,3-di-O-acetylnoviosides from 3-O-acetyl-β-noviose 1,2-(methyl orthoacetate) (XXVIII) (1.0 mole)

Alcohol		Catalyst, 0.05 mole	Solvent	Time, h	relative yield (n.m.r.)		
	moles				XXXIII or XXXVI	XXXIV + XXXV	others
phenol	2.0	$SbCl_5$	CH_2Cl_2	0.5	15	85	-
phenol	2.0	$HgBr_2$	CH_3NO_2	1.5	18	82	-
phenol	20	$HgBr_2$	CH_3NO_2	1.5	36	64	-
β-naphthol	2.0	$HgBr_2$	CH_3NO_2	1.5	<17	83	unidentified
β-naphthol	20	$HgBr_2$	CH_3NO_2	1.5	<45	55	unidentified

XXXIII phenyl 2,3-di-O-acetyl-α-novioside

XXXIV methyl 2,3-di-O-acetyl-α-novioside

XXXV methyl 2,3-di-O-acetyl-β-novioside

XXXVI β-naphthyl 2,3-di-O-acetyl-α-novioside

compounds was obtained (Fig. 35). The first eluted compound was identified by n.m.r. as β-naphthyl 2,3-di-O-acetyl-α-novioside (XXXVI). The interpretation of the n.m.r. spectrum will be discussed later on. The second eluted spot was a mixture of at least two different compounds. The spot gave a coloration of blue on top of brown when the chromatogram was sprayed with vanillin-sulfuric acid mixture (55). The n.m.r. spectrum of this mixture could not be deciphered and, unfortunately, there were aromatic ring proton absorptions at low field which made the calculation of the relative yield of compound XXXVI impossible. The third and fourth eluted compounds were identified by n.m.r. as methyl 2,3-di-O-acetyl-α-novioside (XXXIV) and methyl 2,3-di-O-acetyl-β-novioside (XXXV), respectively. The yield of compound XXXVI was estimated to be less than 17%. This was calculated by comparison of the integration values for the signals of the β-naphthyl ring protons at τ2.30-2.92 in compound XXXVI and the 1-methoxyl protons at τ6.65 in compounds XXXIV and XXXV. Again, judging from the intensity of the spots on t.l.c., compound XXXIV was formed in a larger proportion than XXXV. When 20 moles of β-naphthol per mole of the orthoester (XXVIII) were used, the yield of compound XXXVI was estimated to be less than 45%.

β-Naphthyl 2,3-di-O-acetyl-α-novioside (XXXVI) had $[\alpha]_D^{26}$ -65.5° (c, 1.83 in chloroform); the n.m.r. spectrum

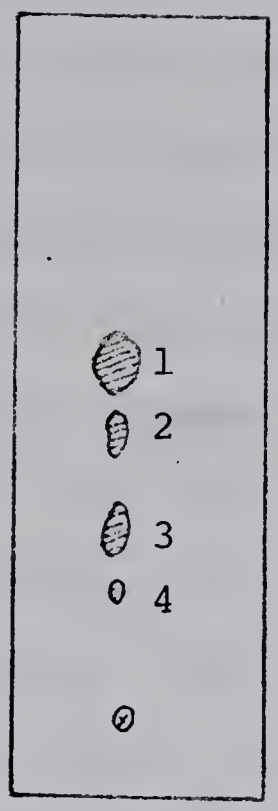


Fig. 35. A thin-layer chromatogram of the condensation product of 3-O-acetyl-β-noviose 1,2-(methyl orthoacetate) (XXVIII) with β-naphthol, using 5% ethyl acetate in chloroform as the developing solvent.

1 β-naphthyl 2,3-di-O-acetyl-α-novioside (XXXVI)

2 unidentified by-product

3 methyl 2,3-di-O-acetyl-α-novioside (XXXIV)

4 methyl 2,3-di-O-acetyl-β-novioside (XXXV)

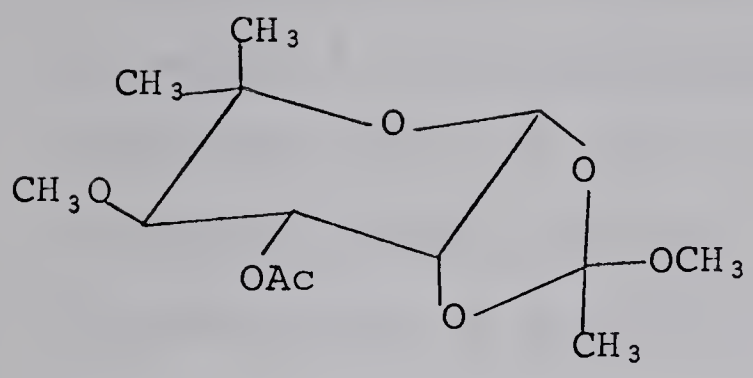


of this compound is shown in Fig. 36. The signal for H-4 is a sharp doublet with a spacing of 10 Hz at τ6.64. Irradiationat this resonance frequency collapsed the quartet at τ4.52 to a doublet with the smaller spacing (3.0 Hz). Therefore, the signal for H-3 must be at this position, and the spacing (3.0 Hz) is the coupling constant of H-3 with H-2. The quartet at τ4.65 was assigned to H-2 with the smaller spacing (2.0 Hz) arising through the coupling of H-2 with H-1. The signal for the anomeric proton is a doublet at τ4.50. The signal for H-3 (τ4.52) was at a lower field than that of H-2 (τ4.65). This is, as mentioned before, due to the deshielding effect of the axial β-naphthyl group at the C-1 position (113, 114). This fact coupled with the large negative rotation of compound XXXVI confirmed the assignment of the β-naphthyl 2,3-di-O-acetylnovioside as the α-anomer.

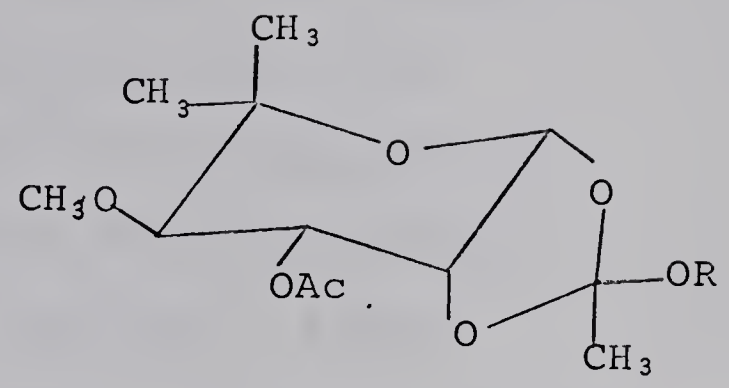
The formation of 2,3-di-O-acetyl-α-noviosides in high yield from the condensation of 3-O-acetyl-β-noviose 1,2-(methyl orthoacetate) (XXVIII) is best appreciated on the basis of dissociation of the orthoacetate, through the agency of the acid catalyst, to the 1,2-acetoxonium ion 1 (Fig. 42) followed by attack by the alcohol at the anomeric center of this ion, as is indicated in Fig. 42 for the formation of compounds XXXIII, XXXIV and XXXVI. The high yields of the methyl 2,3-di-O-acetyl-α-novioside (XXXIV) as compared to the aryl 2,3-di-O-acetyl-α-noviosides (XXXIII or XXXVI) suggest that novioside formation

$$2ROH + A \rightleftharpoons \overset{-}{R}OA + \overset{+}{R}OH_2$$

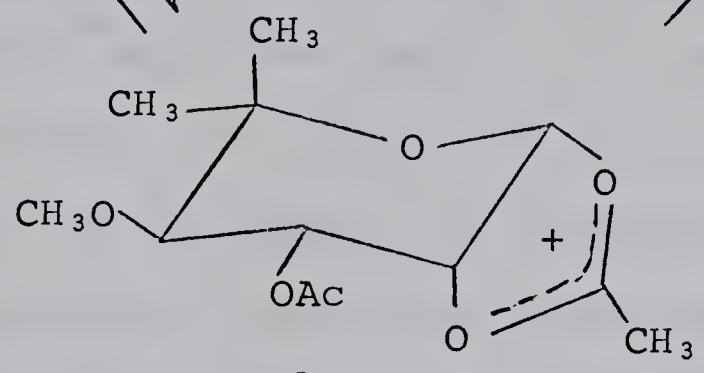
A = $Sbcl_5$, $HgBr_2$ etc.



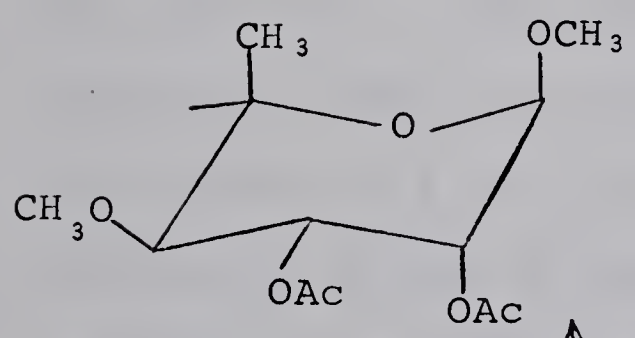
XXVIII



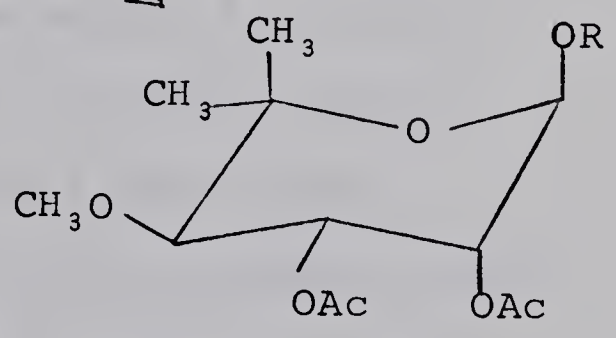
2



1

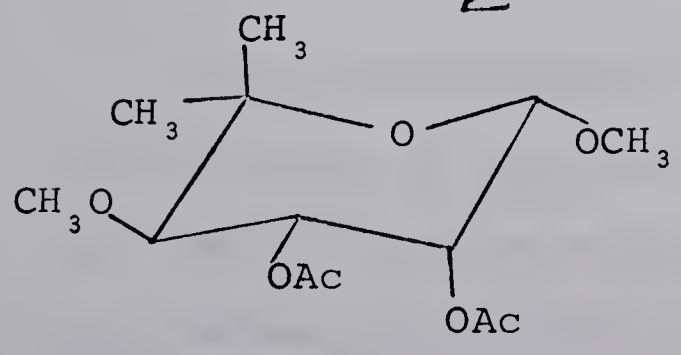


XXXIV

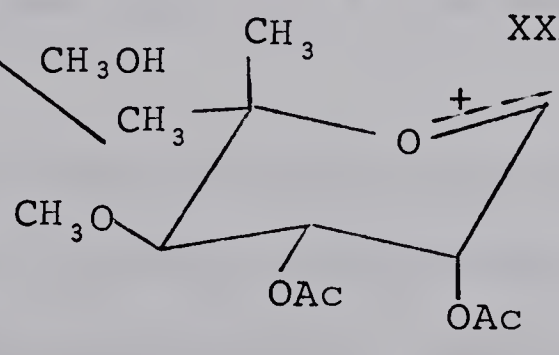


XXXIII, R = C_6H_5

XXXVI, R = β-$C_{10}H_7$



XXXV



3

R = C_6H_5, β-$C_{10}H_7$

Mechanistic considerations in the formation of 2,3-di-O-acetylnoviosides.

was preceeded by a fast equilibration of the orthoesters XXVIII and 2. The relative stabilities of these orthoesters were not determined. However, the formation of methyl 2,3-di-O-acetylnoviosides in good yield, especially when the ratio of phenol (or β-naphthol) to orthoester XXVIII was low, suggests that appreciable concentrations of methanol were developed. Since methanol is undoubtedly a much better nucleophile than is phenol (or β-naphthol), it must be expected that it will compete favorably with the phenol (or β-naphthol) in glycoside formation even though its concentration is much lower than that of the phenol (or β-naphthol). The present results are in line with these expectations.

Relatively small amounts of 2,3-di-O-acetyl-β-noviosides were formed. The aryl 2,3-di-O-acetyl-β-noviosides were not detected in the products but the methyl 2,3-di-O-β-novioside (XXXV) was always present in amounts readily detectable by t.l.c.. This compound may have formed indirectly by way of anomerization of the α-isomer (XXXIV) or directly as indicated in Fig. 42 from the carbonium ion 3 which may have arisen from the 1,2-acetoxonium ion 1.

It is interesting to note that the acid-catalyzed ring opening of 3,4,6-tri-O-benzyl-β-D-mannopyranose 1,2-(methyl orthoacetate) in methylene chloride containing p-toluenesulfonic acid, excluding water or any alcohol,

also produced a small proportion of methyl 3,4,6-tri-O-benzyl-β-D-mannopyranoside (142).

Formation of methyl glycosides from the starting orthoesters limits the yields of aryl α-glycosides obtained by this method. It became evident, therefore, that the preparation of aryl α-glycosides in acceptable yield from methyl orthoacetates would require first the conversion of the methyl orthoacetate to the corresponding aryl orthoacetate with removal of the methanol from the system. This hypothesis was tested as follows:

A mixture of nitromethane containing 3,4,6-tri-O-acetyl-β-D-mannopyranose 1,2-(methyl orthoacetate) (XXX), phenol, and mercuric bromide in 1,2-dichloroethane (see Experimental section XII, 4), was distilled at atmospheric pressure for 1.5 h with addition of fresh solvent so as to keep the volume constant. The isolated product consisted of about 20% phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI) and 80% methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII), as indicated by the n.m.r. spectrum. This result showed that the rate of removal of the methanol was much slower than the rate of formation of glycosides from the orthoesters under the specified conditions.

When a solution in nitromethane of compound XXX and phenol was distilled at atmospheric pressure (see Experimental section XII, 4) to a definite volume,

traces of methanol present in the first fraction of the distillates could be detected by n.m.r. spectroscopy. Part of the residual solution was evaporated *in vacuo* to yield a syrup which contained about 60% of the starting material (XXX), as indicated by the n.m.r. spectrum. Mercuric bromide in 1,2-dichloroethane was added to the remaining solution, and refluxed for 1.5 h. The n.m.r. spectrum showed the product to consist of about 33% phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXI) and 67% methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (XXXII). This result indicated that, in the absence of the acid catalyst, equilibration of the orthoesters occurred, but only traces of methanol were removed from the system. Once the acid catalyst was added, the glycosidation step was very fast. The yield of aryl α-glycosides was substantially improved, but it still left much to be desired.

It appears that a systematic study is required, if the above procedure is to be a useful method for the synthesis of aryl α-glycosides. For example, it might be possible to find a concentration of acid which would allow rapid equilibration of the orthoesters, compared to the rate at which methanol can be removed from the system, but provide a much slower rate of glycoside formation. Once all the methanol was removed, it should then be possible to convert the residue to the aryl α-glycoside in high yield by the introduction of more

acid to enhance the rate of this reaction.

A second method which might result in an acceptable route to aryl α-glycosides from methyl orthoacetates would follow the procedures established by Lemieux and Detert (149), which involve an exchange of the ethyl orthoacetate of D-glucopyranose for either the corresponding 1,2-ketal or 1,2-ortholactone derivatives. Attempts to prepare 3,4,6-tri-O-acetyl-1,2-O-isopropylidene-β-D-mannopyranose from 3,4,6-tri-O-acetyl-β-D-mannopyranose 1,2-(methyl orthoacetate) (XXX) were not successful. The starting material (XXX) was recovered from the reaction which was carried out either at room temperature or at a higher temperature (bath temperature 70°) for 20 h. When more forcing conditions were used by increasing the concentration of the acid catalyst coupled with heating, the reaction gave intractable material. Attempts to prepare 3,4,6-tri-O-acetyl-1,2-O-isopropylidene-β-D-mannopyranose, analogous to the procedure devised by Rees, Tatchell, and Wells (150) for the preparation of 1,2-O-alkylidene-α-D-glucopyranoses from tetra-O-acetyl-α-D-glucopyranosyl bromide and cadmium dialkyls, were no more successful than the exchange method.

In view of these negative results, the mechanism for the formation of 1,2-O-isopropylidene derivative of D-glucopyranose (140) is likely as shown in Fig. 43.

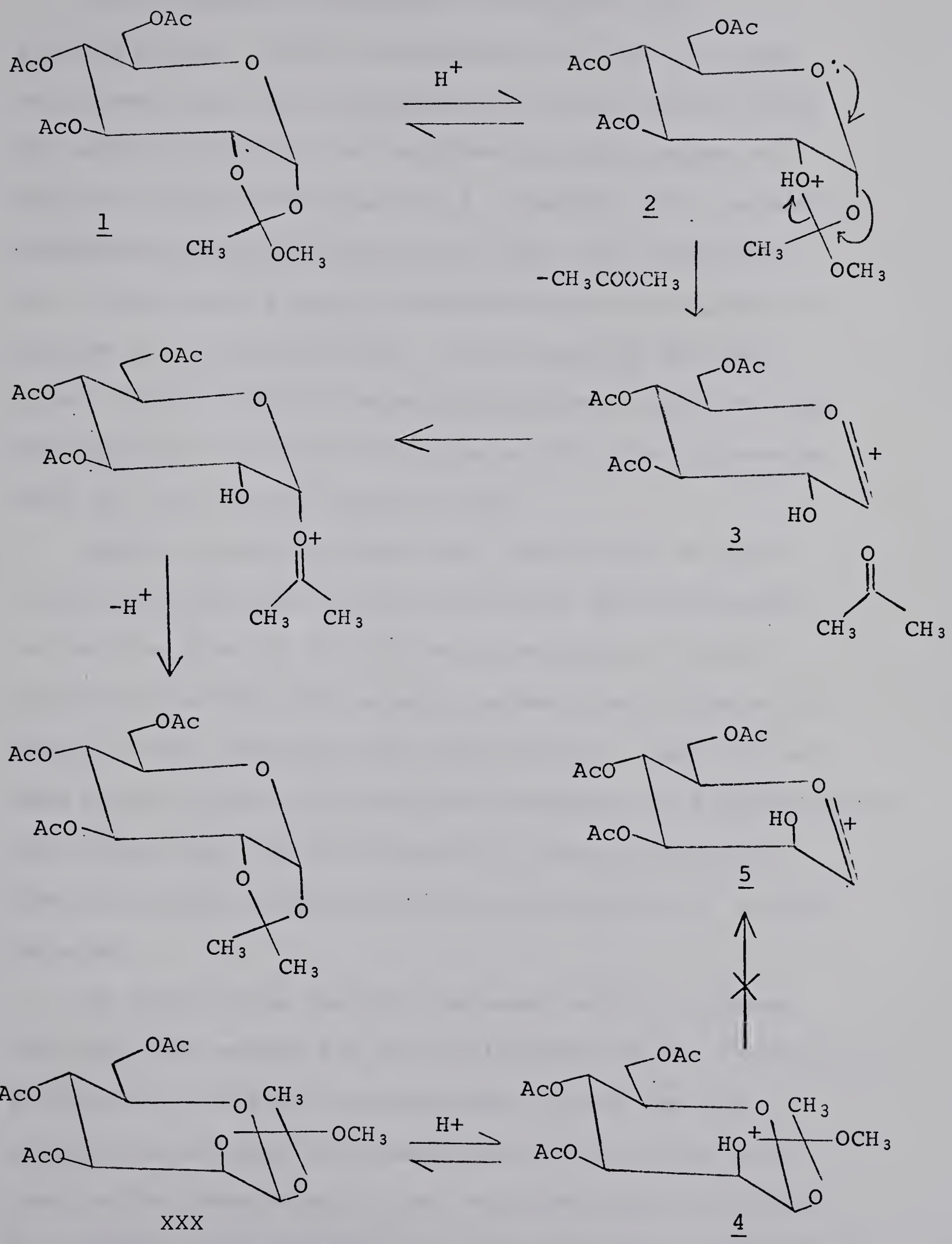


Fig. 43. The mechanism for the formation of 1,2-O-isopropylidene derivative of D-glucopyranose (140).

In the case of the methyl orthoacetate of D-glucopyranose (1), the carbonium ion 2 has the trans arrangement for the elimination of methyl acetate with the participation by the neighbouring ring oxygen to give the cyclic carbonium ion 3. Whereas, for the methyl orthoacetate of D-mannopyranose (XXX), the carbonium ion 4 lacks such a trans arrangement for the elimination to give the intermediate 5. It is possibly for this reason that 3,4,6-tri-O-acetyl-1,2-O-isopropylidene-β-D-mannopyranose could not be prepared from the orthoester (XXX) by the exchange method (149).

Another possible reason for the failure to form 1,2-O-isopropylidene-β-D-mannopyranose derivatives may be that the mannose derivatives have the C_1-O bond equatorial so that the anomeric effect cannot operate to stabilize the isopropylidene derivatives. There do not seem to be any well authenticated examples of isopropylidene derivatives with this conformation prepared directly from free sugars with acetone in the presence of an acid catalyst.

In view of the results discussed above, it seems that the best method for the utilization of the crystalline β-noviose 1,2-(methyl orthoacetate) (XXIX) for the preparation of aryl 3-O-substituted-α-noviosides will involve the conversion of the 3-O-substituted β-noviose 1,2-(methyl orthoacetate) to a 2-O-acetyl-3-O-substituted-noviosyl halide (151) which can then likely be condensed

with the aryl alcohol under the variety of conditions which have been developed for this purpose (139, 152, 153). Normally, the glycosidation is performed in acid media using, for example, mercuric bromide as the catalyst (154, 155). Thus, orthoesters which may form during the course of the reaction would not be expected to survive. Therefore, it should not be necessary to utilize a non-participating group at the 2-position as was done by Vaterlaus and co-workers in their synthesis of novobiocin (I) (24).

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